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A FATAL CASE OF STRONGYLOIDOSIS IN MAN, WITH AUTOPSY

THE LIFE CYCLE OF STRONGYLOIDES INTESTINALIS IN MAN *

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The following report of an acutely fatal case of infestation with *Strongyloides intestinalis* is of interest because the observations seem to throw new light on some obscure problems connected with the disease.

REPORT OF CASE

O. H., an American railroad engineer, aged 36, was born in Texas and lived there all his life until he came to California six months before entering the hospital. On Nov. 25, 1928, he contracted a cold in the chest. Shortly thereafter he began to have a sore mouth and by December 20, had developed a sore throat and hoarseness. On December 29, he began to vomit everything taken by mouth. At the same time he had diarrhea and bled from the anus. He had had a similar attack lasting seven days two years before, while still in Texas.

When he entered the hospital on Dec. 31, 1928, he had a marked stomatitis. The inside of his mouth was covered with white plaques of a pasty exudate, which were easily removed from the underlying red mucosa. The entire buccal cavity was involved. The deposits were most marked along the sides of the mouth, under the tongue and in the tonsillar region, including the pillars of the fauces. Bacteriologic examination showed the presence of streptococci. Spirochetes or fusiform bacilli were not found in the smears. It is doubtful whether the stomatitis had any direct connection with the strongyloidosis.

Nothing abnormal was discovered in the patient's chest and abdomen. The anus was surrounded by an area of excoriation, measuring approximately 2 cm. in diameter. On digital examination, the rectum was found to be tender.

The patient's blood pressure was 130 systolic and 85 diastolic. His blood was practically normal, showing 3 per cent eosinophils on the first examination and later 1 per cent.

He vomited considerable quantities of bile-stained mucus and also had marked diarrhea. His stools were examined twice, on January 6 and 10. They contained no gross admixture of blood or pus, but gave a positive reaction for occult blood. No ova or parasites were discovered, although they were looked for.

The patient vomited so much that he became dehydrated. He remained hoarse and appeared rather dull mentally. His stomatitis gradually subsided.

On Jan. 7, 1929, he complained of itching on the hands, chest and legs.

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On the whole, his condition seemed gradually to improve. He vomited less and was beginning to take a moderate amount of nourishment. His diarrhea had stopped to a certain extent. On January 25, however, he felt weak and complained of impaired vision. He became drowsy and spoke incoherently. On January 27, his condition suddenly became alarming, and he died during the afternoon.

A complete autopsy, including an examination of the brain, was done within a few hours of death. The stomatitis had practically disappeared. The only important lesion in the viscera of the chest was an old chronic myocarditis of the anterior wall of the left ventricle with slight dilatation of the left side of the heart. This had caused a chronic passive congestion of the lungs with the development of many heart failure cells. The small bronchi were filled with thick mucopurulent material, and the pulmonary tissue was excessively inflated with air, probably on account of a partial obstruction of the bronchioles by the sticky exudate in them.

The mucous membrane of the stomach was much congested and covered with a solid layer of gray mucus. The lower mesenteric lymph nodes were moderately swollen and gray on the cut surface. The duodenum and jejunum were much congested. The mucosa of the ileum was dark red and slightly dull on the surface. The large intestine was distended with dark-greenish, soft stools, and its mucosa also showed a diffuse congestion, which was particularly well marked in the lower part of the colon and rectum, where the normal gloss on the surface was partly absent.

The rest of the abdominal viscera were normal, except for the accidental presence of several large false diverticula in the upper part of the jejunum.

The case had been puzzling to the clinicians and was not satisfactorily explained by the gross observations at the autopsy, which, as already indicated, revealed merely the presence of a well marked gastro-enteritis of moderate severity and a healed chronic myocarditis with chronic passive congestion of the lungs, which, however, had not been accompanied by any evident disturbance in the systemic circulation. The infection of the bronchi that was also present was hardly of sufficient severity to explain the death of the patient.

The infestation with *Strongyloides* was not discovered until a microscopic examination was made of the gastro-intestinal tract. Fortunately, on account of the early performance of the autopsy, the tissues were well preserved and showed the finer histologic details clearly.

The mucous membrane of the pyloric region of the stomach was filled with mother worms, ova and rhabditiform embryos. Unfortunately, no pieces for microscopic study had been taken from the duodenum and jejunum. No parasites were discovered in the lower part of the ileum, while the mucosa of the colon contained a considerable number of filariform larvae. A few of them were present in the submucosa and in the muscular coat. The larvae were also found in the swollen lower mesenteric lymph nodes. None were encountered in sections of the lungs and of the liver in spite of careful search of several specimens with microscopes equipped with the mechanical stage.

The presence of the parasites had produced relatively little reaction in the gastric mucosa, which showed a slight irregular infiltration with lymphocytes and eosinophilic leukocytes. The mucous membrane of the ileum, although not containing any parasites, was much congested and filled diffusely with eosinophils. Similar histologic changes were present in the large intestines, in which the eosinophilic infiltration was especially well marked in the immediate vicinity of the filariform larvae, so much so that the accumulations of eosinophils about them materially facilitated their discovery in the sections. The surface epithelium

was almost entirely missing in all sections of the gastro-intestinal tract, but this might have been a postmortem change. The inflamed mucosa was not covered with false membranes, nor was there any evidence of ulceration, even microscopically. The mesenteric lymph nodes showed congestion and a diffuse infiltration with eosinophils. This was especially well marked in the vicinity of the larvae which were contained in them.

COMMENT

In strongyloidosis, the parthenogenic or more probably hermaphroditic (Sandground [1]) mother worms of *Anguillula* or *Strongyloides intestinalis* live in the pyloric part of the stomach, the duodenum and the upper part of the jejunum. As Golgi and Monti [2] first showed, they enter the crypts in order to deposit their ova. This they often do in such a way that their tail ends are folded back and their genital pores exposed at or near the bottom of the invaded crypts. In their progress down the crypts, the worms may pierce the epithelial lining and lie in longitudinal channels within the epithelial cells, or they may compress the epithelium leaving only a narrow border, or they may rub it off entirely from the membrana propria. Askanazy [3] and other investigators were of the opinion that they frequently enter the stroma of the mucous membrane. In my case, careful examination of serial sections did not seem to support this idea. Even when in certain specimens it appeared evident that the worms were outside the crypts, the following sections showed plainly that this was not so and that they were in preformed cavities continuous with the crypts. It is possible, however, that sometimes the mother worms push their way through the thin partition between neighboring glands, coming to lie partly in one and partly in the other, although even this is not certain. I failed entirely to find the open channels that have been described by other authors as being produced by the migrations of the mother worms in the mucosa.

The ova are deposited within the epithelial lining, and the epithelial cells often surround the ova on all sides. Frequently, the ova are behind the epithelium, between it and the membrana propria. The number of ova in each infested crypt varies from one to five. It is evident that the worms can pass from crypt to crypt, probably by withdrawing from one crypt and entering a new one from the lumen, because frequently a series of crypts were seen that contained ova and no mother worms. The ova show all stages of development to the hatching of the rhabditiform embryos. When the latter leave their egg shells, eosinophilic

1. Sandground: Biological Studies on Life-Cycle in Genus Strongyloides Grassi, 1879, Am. J. Hyg. **6**:337, 1926.

2. Golgi and Monti: Sulla storia naturale e sul significato clinico-patologica delle cosi-dette anguillule stercorali e intestinali, Arch. per le sc. med. **10**:93, 1886.

3. Askanazy: Ueber Art und Zweck der Invasion der Anguillula intestinalis in die Darmwand, Centralbl. f. Bakteriol. **27**:569, 1900.

leukocytes are attracted into the crypts. The embryos leave the crypts and enter the intestinal canal. On their way out of the crypts, they pass through the epithelium or through the lumen of the crypts. In a careful study of microscopic sections, I was unable to convince myself that they ever enter the stroma of the mucous membrane.

The embryos travel down the intestinal canal with its contents. In the feces, they change directly into filariform larvae or develop into sexually mature worms, which copulate and produce fertilized ova. The latter develop into rhabditiform embryos, which, in their turn, change into filariform larvae.

The filariform larvae are different from the rhabditiform embryos and, although more difficult to find, can be easily recognized as such in sections. They are more slender and stain less deeply. Darling [4] called attention to the fact that in fresh specimens they have an active boring motion, while the embryos have a slower wriggling motion. The direct transformation of embryos into larvae can take place within the colon, but the sexual development occurs only outside of the body. For unknown reasons, the relative frequency of the sexual and asexual cycles varies much in different cases and probably at different times in the same case, sometimes to the exclusion of one or the other.

Following Loos' discovery of the pentration of the skin by the larvae of *uncinaria*, van Durme [5] showed that the larvae of *Strongyloides* from a chimpanzee entered the skin of guinea-pigs. This observation has since been confirmed in other animals by Kosuge [6] and in man by Fülleborn.[7] The infection can therefore take place either through the skin or by way of the alimentary tract. The larvae that enter the skin are carried by the blood to the lungs and from there they reach the stomach by way of the bronchi, larynx and esophagus. When the larvae arrive in the stomach, duodenum and jejunum, they develop into the relatively large mother worms, which deposit their ova in the manner already indicated.

Fülleborn [7] made the interesting observation that the entrance of larvae into the skin of uninfected persons does not produce any reaction, while in infected persons it causes a marked local inflammation. He believed that carriers of *Strongyloides* are often reinfected through the

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4. Darling: Strongyloides Infections in Man and Animals in the Isthmian Canal Zone, J. Exper. Med. **14**:1, 1911.

5. Van Durme: Quelques notes sur les embryons de "Strongyloides intestinalis" et their pénétration par la peau, Thompson Yates Lab. Rep. **4**:471, 1902.

6. Kosuge: Histologische Untersuchungen über das Eindringen von Strongyloides stercoralis in die Haut von Versuchstieren, Arch. f. Schiffs- u. Tropen-Hyg. **28**:15, 1924.

7. Fülleborn: Hautquaddeln und Autoinfektion bei Strongyloidesträgern, Arch. f. Schiffs- u. Tropen-Hyg. **30**:721, 1926.

skin near the anus by larvae which have developed in fecal remnants in this region. He could not demonstrate any other possibility of reinfection and came to the conclusion that the host apparently produces antibodies which stop the development of the larvae.

Imperfect histologic studies of the disease in man were made by Normand [8] in 1876. It was he who discovered the parasites in the stools of soldiers returning to France suffering from Cochin-China diarrhea. On the basis of his investigations, he suspected that the worms enter the crypts of the intestine. In 1886, the problem of their relation to the mucosa was attacked with modern methods by Golgi and Monti,[2] who were followed by Riva [9] in 1892, Askanazy [3] in 1900, Strong,[10] Thayer [11] and von Kurlow [12] in 1902, Brown [13] in 1903, Darling [4] and Gage [14] in 1911, and Oudendal [15] in 1926. A fatal infection with *Strongyloides* in a chimpanzee was described in 1922 by Blacklock and Adler.[16] It is of special interest on account of a tumor-like hyperplasia of the mucous membrane in part of the infected region, and also on account of the fact that the chimpanzee died of an acute general infection with the larvae, which were found in the lungs, in which they had produced multiple hemorrhages, and in the bronchi, the pericardium, the spleen and the blood of the right ventricle. Blacklock and Adler [16] surmised that a sufficient number of larvae to cause the fatal infection by way of the skin must have lodged in the crevices of the wooden cage of the animal. In 1923, the intestinal lesions in *Macacus* were studied by Hung-See-Lü and Höppli.[17]

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8. Normand: Sur la maladie dite diarrhée de Cochinchine, Compt. rend. Acad. d. sc. **83**:316, 1876.

9. Riva: Sopra un caso di anguillulosi intestinale sperimentale, Arch. di biol. **46**:40, 1892.

10. Strong: Cases of Infection with Strongyloides Intestinalis, Johns Hopkins Hosp. Rep. **10**:91, 1902.

11. Thayer: On the Occurrence of Strongyloides Intestinalis in the United States, J. Exper. Med. **6**:75, 1901-1905. Strong and Thayer reported the same case. Thayer gave an excellent historical review of the subject to 1902.

12. Von Kurlow: Anguillula intestinalis als Ursache akuter, blutiger Durchfälle beim Menschen, Centralbl. f. Bakteriol. **31**:614, 1902.

13. Brown, P. K.: The Report of Three Cases in Which Embryos of the Strongyloides Intestinales Were Found in the Stool: Autopsy of One Case, Boston M. & S. J. **148**:583, 1903.

14. Gage: A Case of Strongyloides Intestinalis with Larvae in the Sputum, Arch. Int. Med. **7**:561 (April) 1911.

15. Oudendal: Die Darmwand bei Anguilliasis intestinalis, Arch. f. Schiffs- u. Tropen-Hyg. **30**:510, 1926.

16. Blacklock and Adler: The Pathological Effects Produced by Strongyloides in a Chimpanzee, Ann. Trop. Med. **16**:283, 1922.

17. Hung-See-Lü and Höppli: Morphologische und histologische Beiträge zur Strongyloidesinfektion der Tiere, Arch. f. Schiffs- u. Tropen-Hyg. **27**:118, 1923.

The descriptions of the different investigators in regard to the entrance of the mother worms into the crypts, the deposition of the ova and the development of the embryos agree in a general way. Most authors were of the opinion that both the mother worms and the embryos can enter the stroma of the mucous membrane, and Oudendal [15] insisted that this is the usual path for the return of the embryos to the lumen of the intestine. It is generally agreed that neither mother worms nor embryos can penetrate beyond the muscularis mucosae. As stated, in my case I was unable to find certain evidence that the worms or the embryos ever leave the crypts, although they were often shown penetrating the epithelium and causing a partial destruction of the epithelial lining.

The infestation is usually limited to the pyloric end of the stomach, the duodenum and the upper part of the jejunum, although Riva [9] found mother worms and embryos in the mucosa as far down as the cecum, but none below this point. Von Kurlow [12] reported the presence of a few small worms in the mucous membrane of the colon. It is uncertain whether these were embryos or larvae. Darling [4] made the positiv statement that the strongyloides do not invade the mucosa of the large bowel and that for this reason they cannot be incriminated as a causative agent in diarrhea.

What in the end becomes of the mother worms is not known. Probably they die and disintegrate in the intestinal contents; at any rate, dead mother worms have never been discovered in the intestinal wall and have only rarely been found in the stools.

The filariform larvae have not been identified in the intestinal wall except in the remarkable fatal case reported by Gage,[14] in which during life larvae were present in the sputum. In microscopic sections in this case, they were seen deep in the lymph spaces of the wall of the duodenum and jejunum and in the alveoli of the lungs. The transformation of the embryos into the filariform larvae must have taken place immediately in the upper intestine. An invasion of the wall of the colon is not mentioned. From the description, it is not clear whether the colon was examined microscopically. A similar penetration of the intestinal wall by the larvae probably also had occurred in Teissier's [18] case; Teissier found them in the blood of a patient suffering from infestation of the intestines by *Strongyloides*. In the case of a general infection of a chimpanzee with larvae, Blacklock and Adler [16] assumed that the larvae had entered the circulation through the skin after having developed in the crevices of a wooden cage—which seems unlikely.

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18. Teissier: Contribution a l'étude de l'anguillule stercorale. De la pénétration dans le sang des embryons de l'anguillule stercorale, Arch. de méd. expér. et d'anat. path. **7**:675, 1895.

Gage [14] pointed out that the long persistence of the disease presupposes constant reinfection, and he believed that, although in his patient reinfection from the skin was probable on account of the filthy condition, it also occurred, perhaps to a greater extent, from the intestines by way of the thoracic duct.

The discovery of the larvae in the wall of the colon and in a mesenteric lymph node in my case is important for two reasons. In the first place, it confirms Gage's idea that reinfection in strongyloidosis can take place from the intestines, and second, it explains the occurrence of colitis and diarrhea in connection with the disease. I think that a transformation of the rhabditiform embryos into filariform larvae occurs more commonly in the colon, as in my case, than in the small intestine, as in Gage's [14] case. Probably in the colon it is a constant occurrence. The entrance of some of the larvae into the blood vessels supplies a limited number of new mother worms, and this accounts for the indefinite persistence of the infection. When the larval invasion is unusually marked in a sensitized person colonic irritation results, followed by diarrhea. This was evidently so in my case, in which the number of filariform larvae in the mucous membrane of the colon was large. In the spots of heaviest infestation, a half dozen, at least, were present in each section which, when a similar distribution prevails over a piece of the colon of any size, means the presence of an enormous number. Only relatively few of them, however, had succeeded in entering the submucosa by penetrating through the muscularis mucosae. The majority of them were found coiled in the stroma of the mucous membrane in front of this obstacle. The unsuccessful ones probably finally die, disintegrate and are absorbed. The specimens leave no doubt as to the actual invasion of the stroma of the mucous membrane.

In the ordinary course of events the infestation persists indefinitely with occasional attacks of diarrhea or without any symptoms. When, for unknown reasons, an unusually large number of embryos within the intestinal tract change into filariform larvae and enter the intestinal wall in the region of the colon, a severe colitis with a marked infiltration of the mucosa with eosinophilic leukocytes is produced. In exceptional cases, this is accompanied by so massive a general invasion of the body with larvae that death results. From my observations and from others reported in the medical literature it would appear that sometimes under these circumstances practically all of the embryos in the intestinal contents become larvae and invade the bowel wall, with the result that not any or only a few parasites are present in the fecal discharges.

The occurrence of the severe, fatal infestations that have been mentioned in this article makes it evident that, in spite of the usual absence of alarming symptoms, strongyloidosis must be regarded as a serious

disease. It was looked on as such by Barlow,[19] who had the opportunity of studying a series of twenty-three cases in Central America. He described a first stage of invasion, which is usually accompanied by marked symptoms; a second, latent stage, which may last for many years and in which there are no serious symptoms while the parasites continue to be present in the stools; a third stage of diarrhea and a final stage of neurasthenia.

In my case, the attack was evidently a recurrent one, because the patient had had similar manifestations two years before when still living in Texas. It is improbable that he contracted the disease during his stay in California. His death must be directly ascribed to the infection with *Strongyloides*. A general lack of resistance due to chronic myocarditis may have contributed to the fatal outcome, but there was no evident disturbance of the general circulation, nor did he die from cardiac disease.

CONCLUSIONS

Strongyloidosis, although usually not accompanied by serious symptoms, may produce severe disturbances and occasionally death.

In this disease, autoreinfection takes place constantly by the entrance of filariform larvae through the skin, especially in the region of the anus, or by their invasion of the intestinal wall, usually in the region of the colon and rectum. From the colon and upper part of the rectum, the larvae are carried to the lungs indirectly by way of the thoracic duct, while those that penetrate the lower part of the rectum can reach the lungs directly by way of the lower hemorrhoidal veins. The direct mode is probably the more important one, because on the long indirect way many larvae must be destroyed before arriving in the lungs.

The diarrheal attacks are due to an inflammatory irritation of the colon caused by its invasion by the larvae. As usual in infections with animal parasites, their entrance into the tissues is accompanied by a marked local eosinophilia. In spite of the large collection of eosinophils locally, the general eosinophilia is not, as a rule, pronounced.

I have been unable to convince myself that either the mother worms or the rhabditiform embryos ever enter the stroma of the mucous membrane. They cause, however, much epithelial destruction. No evidence has been found that the mother worms become embedded permanently in the mucosa.

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19. Barlow: Clinical Notes on Infection with Strongyloides Intestinalis, Based upon a Series of Twenty-Three Cases, Interstate M. J. **22**:1201, 1915.

MALIGNANT RHABDOMYOMA OF THE LEFT LEG*

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The rarity of tumors originating in striated skeletal muscle has been emphasized recently in the reports by Wolbach[1] and Dewey.[2] In considering the previous accounts of these tumors, Dewey arranged the voluntary striated muscle tumors into two groups: (1) those arising in tissues and organs that normally have no striated skeletal muscle and hence are heterotypic or teratomatous, as in the urogenital tract, the parotid gland and the lungs; and (2) those in the voluntary striped muscle, such as the tongue, lip and skeletal muscles. The latter are the rarer, and of these the frankly malignant tumors are few. The reports of such malignant tumors in man with the details of postmortem examination dwindle to a surprisingly small number. Burgess,[3] in 1913, described extensive metastases in the body of a woman, aged 19, secondary to a primary growth, which the author believed originated in the extensor muscles of the right thigh. He stated in this report that the only other account of a similar tumor had been recorded by Adami who found the tissues in a trout. Burgess[3] at that time could find no description of malignant rhabdomyoma with metastases in man. Martin and Alexander,[4] in 1924, published the clinical and postmortem observations of a malignant rhabdomyoma originating in the soft palate of a girl, aged 6 years. While removing the tonsils of this child, a large mass unlike adenoid tissue was discovered in the nasopharynx. The diagnosis of rhabdomyoma was made from microscopic preparations of a small portion. A more careful examination later demonstrated that the new growth had arisen from the upper and posterior portion of the soft palate. Four months after the tumor was found, the left cervical lymph glands had become enlarged and the mass in the palate had grown so as to obstruct markedly the nasopharynx. The lymph glands, the soft

* Submitted for publication, March 5, 1929.

* From the Henry Baird Favill Laboratory and the Surgical Service "A" of St. Luke's Hospital.

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1. Wolbach, S. B.: A Malignant Rhabdomyoma of Skeletal Muscle, Arch. Path. **5**:775 (May) 1928.

2. Dewey, K. W.: Rhabdomyoma of the Tongue, Arch. Path. **3**:645 (April) 1927.

3. Burgess, A. M.: Malignant Rhabdomyoma with Multiple Metastases, J. M. Research. **29**:447, 1913-1914.

4. Martin, G. E., and Alexander, W. A.: A Case of Rhabdomyosarcoma of the Soft Palate, J. Laryng. & Otol. **39**:312, 1924.

palate and the regional extensions around the eustachian tube were removed surgically. Three weeks later, an aural polyp was excised. Treatment with radium failed to stem the progress of the tumor and death occurred six months after the growth was discovered in the soft palate. While the tissues which were first removed and examined contained structures that Martin and Alexander [4] considered to be of muscular origin, those removed later had the appearance of a spindle cell sarcoma but also included cells which were thought to be of muscular origin. According to their statements, Martin and Alexander [4] would have been unable to establish the muscular origin of this tumor had not the tissues originally removed surgically been available. Additional information obtained by postmortem examination was not included in their report. They referred, also, to a rhabdomyosarcoma of the nasopharynx described by Richardson.[5]

Among the nine cases accepted by Küttner and Landois [6] as rhabdomyomas of skeletal muscle, those reported by Ribbert,[7] Zenker (Bayer) [8] and Fujinami [9] seemed to be definite instances of a malignant growth, because of either recurrence or histologic structure interpreted by the authors as malignant. These reports, however, are based only on the study of tissues obtained surgically. Other accounts of malignant skeletal rhabdomyomas in tissues removed surgically are by Muller,[10] Nicory,[11] Wolbach [1] and Wagner.[12] The tissues studied by Muller [10] were from the right thigh of a man, aged 48; those studied by Nicory,[11] from the uvula of a girl, aged 5 years; the ones by Wolbach,[1] from the dorsal muscles of the chest of a girl, aged 4 years, and those by Wagner,[12] from the right buttock of a man, aged 40 years. The ultimate fate of the patients from whom the tissues were removed was not stated in any of these accounts except Wolbach's; in this instance death occurred after three months. The mixed tumor of the triceps

5. Richardson, in von Bermann: System of Surgery, 1904, vol. 1.

6. Küttner, H., and Landois, F.: Die Chirurgie der quergestreiften Muskulatur, Deutsche Ztschr. f. Chir. **25**:1, 1913.

7. Ribbert: Beiträge zur Kenntniss der Rhabdomyome, Virchows Arch. f. path. Anat. **130**:249, 1892.

8. Zenker, K.: Ein Fall von Rhabdomyosarcom der Orbita, Virchows Arch. f. path. Anat. **120**:536, 1890.

9. Fujinami, A.: Ein Rhabdomyosarcom mit hyaliner Degeneration (Cylindrom) im wilkürlichen Muskel, Virchows Arch. f. path. Anat. **160**:203, 1900.

10. Muller, H. R.: Traumatic Rhabdomyosarcoma Following Successive Fractures of the Femur, J. Cancer Research **2**:393, 1917.

11. Nicory, C.: Rhabdomyoma of the Uvula, with a Collection of Cases of Rhabdomyoma, Brit. J. Surg. **11**:218, 1923-1924.

12. Wagner, J. H.: Rhabdomyomsarcoma of the Buttock, Atlantic M. J. **31**: 570, 1928.

muscle of the right arm reported by Johan [13] was considered by him to have arisen in misplaced somatopleura. Reference is made in this account to reports of similar tumors by Buhl, F. Marchand, Mohr and Lambl.

Burgess [3] described the tissues in his tumor as composed of cells with large vesicular nuclei and a relatively small amount of cytoplasm, about the size of a polymorphonuclear leukocyte. Many were in mitosis. In certain places there were large cells, some multinucleated and containing a large amount of acidophilic cytoplasm. These cells ranged in size between three and six times the diameter of a leukocyte; the nuclei were grouped along the periphery. Among the tapering cells with longitudinal fibrils were some with cross-striations. Burgess stated that he experienced some difficulty in demonstrating cross-striations in the cells. Martin and Alexander,[4] in their report, said that the first tissues removed were myxomatous, but that fibers were included which differed only a little from adult skeletal muscle cells, and that there were many spindle-shaped cells with acidophil cytoplasm and long-tailed ends. Large cells, frequently multinuclear, varying greatly in size, shape and staining reaction, were outstanding structures. Some of these resembled a tadpole in shape, with several nuclei in the "head" and abortive striations of the "tail." Others were round or oval and contained as many as seven round or oval nuclei. The tissues removed later had the structure of a spindle cell sarcoma, but certain cells were differentiated somewhat into muscle fibers.

The tissues described in the earlier accounts (Ribbert, Zenker and Fujinami) contained spindle-shaped cells with cross-striations, as did those reported by Nicory. The tumor recorded by Muller had interlacing bundles of long fusiform cells resembling skeletal muscle and many mononuclear or multinuclear giant cells. Cross-striations were not demonstrated. Wolbach found spindle cells with definite cross-striations in the tumor that he described. He suggested that the myofibrils originate in the centrioles, and that in the absence of definite cross-striations, these tumors may be identified by establishing the presence of centriole clusters and abortive formations of fibrils.

The following account is distinctive in that the myogenic nature of the tumor was recognized in metastases of lymph glands removed several months before the patient died, and because extended observations were made of the disease in many parts of the body by postmortem examination and subsequent histologic studies.

REPORT OF CASE

J. B., aged 6½ years, was admitted to the surgical service of Dr. L. L. McArthur on June 6, 1928, because of a painful, hard, uncircumscribed swelling

13. Johan, B.: Ein Rhabdomyosarcoma Chondro-myxomatosum des Oberarmes, Frankfurt. Ztschr. f. Path. **22**:50, 1919.

in the muscular attachment of the left achilles tendon, and a mass the size of a hen's egg in the left groin. The parents made an indefinite statement concerning a bruise of the leg in July, 1927. About that time, however, a hard mass in the leg was first noted. A physician regarded this as a hematoma, but tissues removed in December, 1927, were diagnosed sarcoma. In April, 1928, the mother noticed a firm mass in the left groin which progressively increased in size. For about two weeks before admission, the boy complained of pain in the left leg, and the mother thought the leg had increased in size. The notes on the physical examination made June 6, 1928, include no important details, except mention of the firm enlargement of the left leg and the mass in the left groin. This mass was removed on June 23, 1928. It was ovoid, encapsulated and 5 by 3 by 2.5 cm. The surfaces made by cutting were white, opaque, firm tissue, mottled somewhat by faintly yellow regions (necrosis) about 1 mm. in diameter.

Histology of the Lymph Gland Tissue.—A stroma of delicate fibrous connective tissue formed the supporting framework of the tumor. In the compact portions, the cells between the stroma fibrils were from 10 to 15 microns in diameter. They had large, oval or indented vesicular nuclei with several coarse chromatin granules, and only a narrow margin of granular cytoplasm. These cells were definitely arranged around capillaries which, with the intimately arranged stroma, accompanied the cells in all parts of the tumor. In less compact portions, especially near necrotic foci, there were large round or oval cells, from 30 to 40 microns in diameter with a granular acidophilic cytoplasm and a single, large round or oval vesicular nucleus, or several nuclei not as large, without regular distribution. Along the edge of the cytoplasm was a narrow layer of refractile substance resembling the ectoplasm of an ameba. The finer details of the structure of the cytoplasm varied considerably. The cytoplasm of some cells contained a few coarse basophilic granules or fine threadlike structures, while that of other cells was drawn out into long slender or short plump prolongations with fine longitudinal striae mottled with alternating delicate light and dark bands like the cross striations of skeletal muscle fibers. These cross striations were especially distinct in large spindle-shaped cells, as long as 170 microns (fig. 1). The single large vesicular nucleus with coarse chromatin granules, usually in the center of the fiber, made an abrupt nodal enlargement of the cell. Short segments of fibrils with cross striations were found without regularity in a variety of places, representing, no doubt, portions of cells the nuclei of which were not in the plane of the sections. Bands of protoplasm were found suggesting skeletal muscle fibers, 70 microns long and from 15 to 20 microns wide, with several nuclei arranged along the periphery. Many cells in mitosis were found. Certain of the finer details of cell structure mentioned were demonstrated in a striking way in sections stained with phosphotungstic acid-hematoxylin.

Because of the presence of these fibrillar structures with cross-striations in tumor tissues metastatic in a lymph gland, a place where one does not regularly find skeletal muscle fibers and which, if present, might alter the conclusion that the spindle-shaped structures mentioned were tumor cells and not inflammatory or retrogressive changes of the skeletal muscle ingrown with tumor, the diagnosis "metastatic rhabdomyosarcoma of the groin lymph glands" was made. The blood on June 9, 1928, had 3,500,000 erythrocytes and 7,600 leukocytes per cubic millimeter, and the hemoglobin was 65 per cent. Dr. E. L. Jenkinson reported, from roentgen films, some destruction of the left os calcis, but no shadows that suggested a growth from the bones. The patient received roentgen treatments and was discharged from the hospital on July 11, 1928, but returned from time to time for further radiation therapy. On Oct. 29, 1928, he was readmitted. The left leg had

swollen so that it was three or four times as large as the right. The left leg was hard and in the upper part of the thigh was a firm mass that extended into the inguinal region. A loss of 6 pounds in weight had occurred. The blood on Oct. 30, 1928, contained 3,310,000 erythrocytes and 7,150 leukocytes, and the hemoglobin content was 63 per cent. On Nov. 29, 1928, Dr. Jenkinson reported definite changes of both lungs, especially of the left lower lobe in roentgenograms, which he interpreted as tumor metastases. There was a slight daily fever ranging between 98.8 and 100 F.; it was somewhat higher during the three days before Nov. 27, 1928, when the patient was taken home for a few days. He returned on Nov. 30, 1928, without appreciable change in his physical condition. The left leg increased in size, tumor nodules appeared in the tissues of the abdominal wall, and apathy, weakness and emaciation increased until death on Jan. 16, 1929, at 12:25

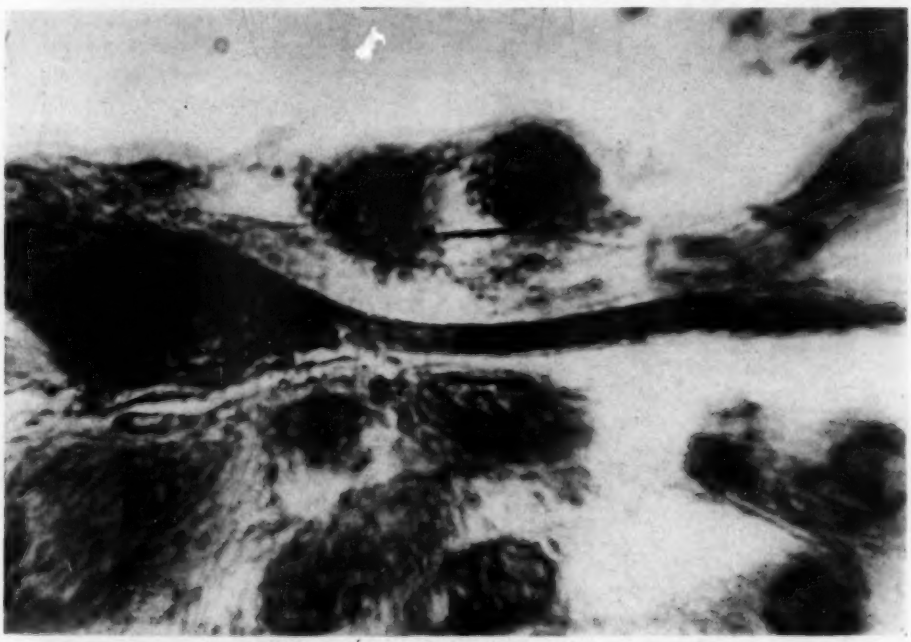

Fig. 1.—A large spindle-shaped cell with cross-striations found in the groin lymph gland removed during life; × 1,730.

a. m. Postmortem examination of the trunk and left leg was made eight hours later. The essential features of the anatomic diagnosis are: huge primary rhabdomyosarcoma of the left leg with marked extension into the left thigh; extensive metastases of the inguinal, pelvic, periaortic, mesenteric, retroperitoneal, biliary, perisplenic, mediastinal, peribronchial, and left axillary lymph glands, and of the lungs, the urinary bladder, the abdominal wall, the skin of the penis and scrotum, and the tissues of the left side of the chest; sarcomatous erosion of the ramus superior of the left os pubis and of the left fibula; bilateral hydronephrosis and hydroureter; marked edema of the left leg and thigh and slight edema of the right; sarcomatous ulcerations of the lining of the inferior vena cava; marked dilatation of the superficial veins of the chest; bilateral hemorrhagic hydrothorax, and marked emaciation.

Only the pertinent statements of the descriptive portions of the postmortem record are included. The hugely enlarged left lower extremity, flexed at the knee, had a diameter of 18 cm. in the middle of the thigh and a dorsoventral thickness of 17 cm. in the center of the leg. The corresponding dimensions of the right lower extremity were 11 and 7 cm., respectively. The skin of the left leg was tense and pebbled like hog's skin; that of the thigh was elevated by many subcutaneous nodules of tumor tissue ranging in size up to 25 mm. in diameter. In the lower three fourths of the thigh these were confluent, but in the upper one fourth they were discrete. Their distribution was chiefly along the front, medial and lateral portions of the thigh. A region of skin tissue 11 by 17 cm. on the front and inside of the middle of the thigh was ulcerated. The nodules in the subcutaneous tissues and skin extended nearly to the costal arch on the left side of the abdomen. They involved the scrotum, the shaft of the penis and the right groin. The superficial veins of the front of the chest were markedly dilated. There were several enlarged lymph glands in the base of the left axilla near the anterior border. The subcutaneous fat in the midline of the trunk was practically absent. In the front midline incision beginning 4 cm. above the umbilicus and extending down to the symphysis pubis were discrete masses of soft white tissue as large as 2 cm. in diameter, making an almost continuous chain, those below having the largest dimensions. The lymph glands of the right axillary fossa were small but in the left, as noted, were several enlarged glands, in all a mass 5 by 3.8 by 2 cm. Some of these were grayish-pink lymphoid tissue with discrete masses of white tumor substance. Extending up from the small pelvis in the midline and lying chiefly on the left side was a mass of soft white tumor tissue 9 by 8 by 6 cm. It occupied a position corresponding to the urinary bladder and was continuous on the left side into the groin. The rectum and sigmoid colon were behind and not attached, although the rectum was markedly compressed. The tissues of the left groin were extensively ingrown with tumor tissue; those of the right, less extensively. The spleen was not enlarged. In the omental fat near the hilum were small masses of white tumor tissue as large as 1 cm. The mesenteric lymph glands were not enlarged. In the periphery of the abdominal surface of the right leaf of the diaphragm were a number of small, flat, pearly thickenings, but there were none in the left half. A small amount of bloody fluid was found in the right pleural cavity, about 200 cc. in the left. There were no adhesions between the parietal and visceral pleura. In the region of the thymic body were two masses of pinkish-white tissue, the left mass 4.5 by 3.3 by 2.2 cm., the right 3.3 by 3 by 2.2 cm. Some portions of these were dark red with recent hemorrhages. Careful examination of the ribs after the chest and abdomen had been eviscerated failed to disclose tumor masses in them but in the soft tissues just below the tip of the left twelfth rib was a mass 1.5 by 1.5 by 1 cm. The lining of the thoracic duct was smooth; the lumen was about 1 mm. in diameter. In the upper thoracic levels in close approximation to the thoracic duct channel was a tumor mass 3.5 by 1.5 by 1.5 cm. The lining of the receptaculum chyli was smooth but the lumen was dilated; it was embedded in masses of lymph glands markedly enlarged by tumor tissue. The thoracic, and especially the abdominal, periaortic lymph glands, were markedly enlarged by tumor tissue and, with tissue in the small pelvis, they formed a huge pyramidal-shaped mass 16 cm. long, 9 cm. wide and 4 cm. thick at the base. They were directly attached to the periosteum of the spinal vertebrae and did not penetrate the bone tissues here. Most of the superior ramus of the left os pubis, however, was destroyed. The parabronchial lymph glands, and the biliary, and peripancreatic lymph glands were markedly enlarged and ingrown with tumor tissue. At the upper pole of the left kidney in

the fat was a pyramidal-shaped, discrete mass of tumor tissue 3.8 by 3.5 by 2 cm. The right lung weighed 180 Gm. The pleura was glistening and smooth. The outlines of the lung lobules were traced in fine black lines of carbon pigment. The lung substance proper was grayish pink and fluffy, except in many discrete nodular regions containing grayish-white tumor tissue, ranging from a few millimeters to 2.5 cm. in diameter and forming about 50 per cent of the entire lung substance. The left lung weighed 400 Gm. and was much more extensively consolidated by tumor tissue. At least four fifths of the lower lobe was solid with tumor, and in the upper lobe were many discrete nodules as large as 1 cm. in diameter. Both lungs were inflated and fixed in formaldehyde. After hardening they were bisected in a plane through the hilum to the periphery. The lower portion of both ureters was greatly compressed by the pelvic tumor tissues and the portions of ureters above were markedly dilated as were both renal pelves and

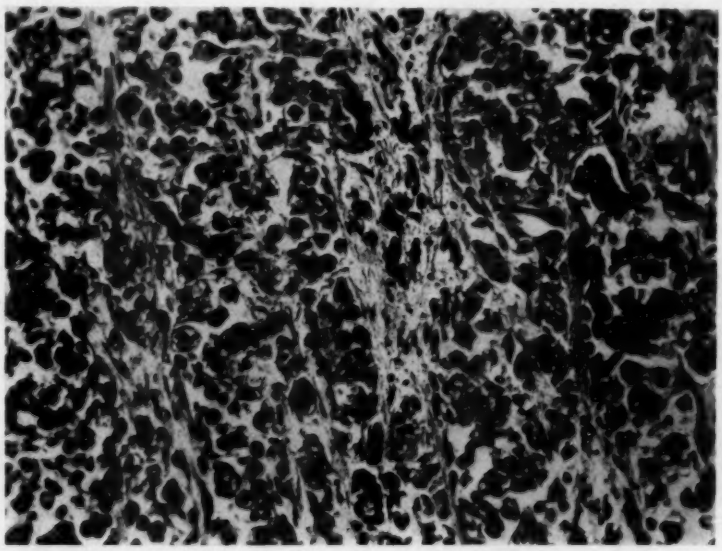

Fig. 2.—The metastatic tumor tissue in a parabronchial lymph gland, illustrating the compartments formed by connective tissue septums, the arrangement of cells along these septums and the variations in the size and shape of the cells; × 151.

the major and minor calices of the kidneys. The right kidney without the capsule and pelvic fat weighed 70 Gm., the left, 60 Gm.

The wall of the urinary bladder was markedly ingrown with white tumor tissue. The inferior vena cava was encased in the enlarged periaortic abdominal lymph glands, and in two places, 3 and 5 mm. in diameter, in the lower portion in front the wall was ulcerated.

On the surfaces made by a deep incision in the front of the left thigh from the groin to the knee and continued through the left leg there was no red muscle tissue, but instead the entire soft parts were lobulated soft white tumor tissue, wet with huge quantities of serous fluids. The shafts of the femur and of the tibia were smooth; the fibula was roughened and eroded.

In the detailed procedure of the necropsy, careful examinations were made of other structures such as the azygos and innominate veins, the aorta and its large

branches, the heart structures, the superior and inferior cavae and their branches, the pulmonary artery and veins, the suprarenal glands, the bile ducts and gall-bladder, the portal vein and its tributaries, the pancreas and its duct, the spleen, the liver (no metastases), the esophagus, the stomach, the small and large bowel (opened lengthwise), the rectum, the appendix vermiformis, the testes, the prostate, the seminal vesicles, the urinary bladder and the bones in general. The head and neck were not opened. Certain of the tissues of the neck were inspected from below; palpation revealed no enlarged cervical lymph glands.

Histology.—Paraffin sections were prepared of tumor tissues in the left leg and thigh, the metastases of the parabronchial, peripancreatic, periaortic and left

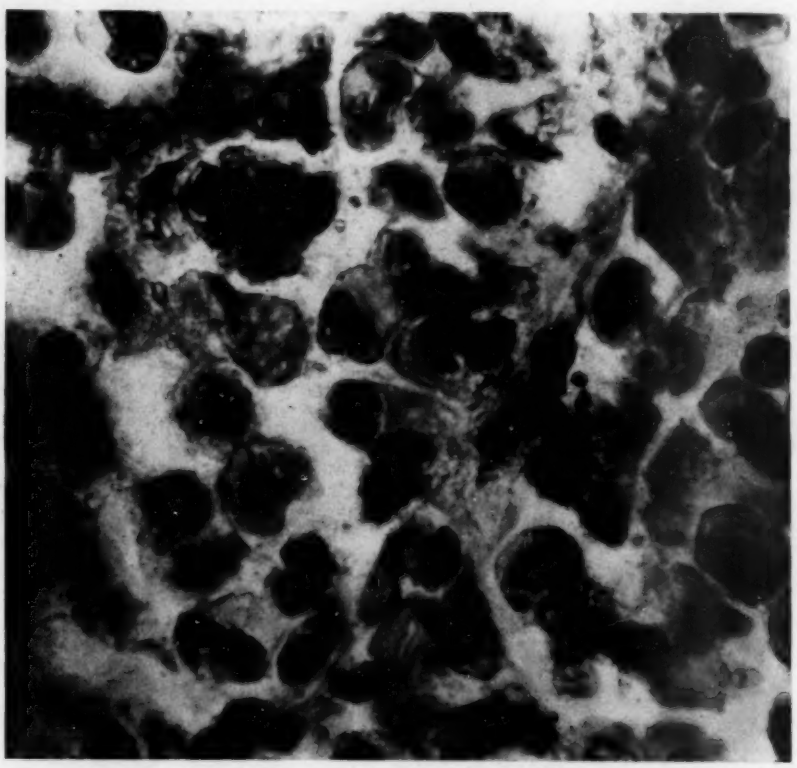

Fig. 3.—Some of the cellular portions of tumor tissue containing chiefly large round cells. Much glycogen was contained in the cytoplasm of such cells; × 1,200.

axillary lymph glands, of the secondary growth near the left kidney, of the left lung and of the nodules in the midline incision of the abdomen. These sections were stained with hematoxylin and eosin, and with phosphotungstic acid-hematoxylin. There was little difference in the tumor tissues in the various sites. The variations were largely in the proportion of the various cellular constituents, the amount and arrangement of the accompanying stroma, and the changes caused by edema or necrosis. Metastases in certain of the lymph glands lend themselves best to the description because the changes due to edema and necrosis were absent; for this reason, the structure of the metastases in the parabronchial lymph glands is given as representative of the tumor.

The structure of the lymph glands was completely replaced by tumor tissue. The more obvious supporting fibrous stroma was in narrow bands, so arranged and interwoven as to form compartments 0.1 mm. and less in diameter resembling the coarse pattern of lung tissue (fig. 2). Small capillaries extended through these narrow collagenic connective tissue septums. In some places this pattern of delicate connective tissue septums had a marked resemblance to the stroma of a highly papillary epithelial growth. Within the compartments were masses of cells, compactly or loosely arranged. They varied considerably in size and shape, not only within each compartment, but in these descriptive units, in various parts of the tumor. Round, oval or elongated cells were the most common, many about 15 microns in diameter, some smaller and others slightly larger (fig. 3). They had an abundant acidophilic, granular cytoplasm, and usually a single large vesicular nucleus, round, oval, indented or lobed, with coarse chromatin granules. Because

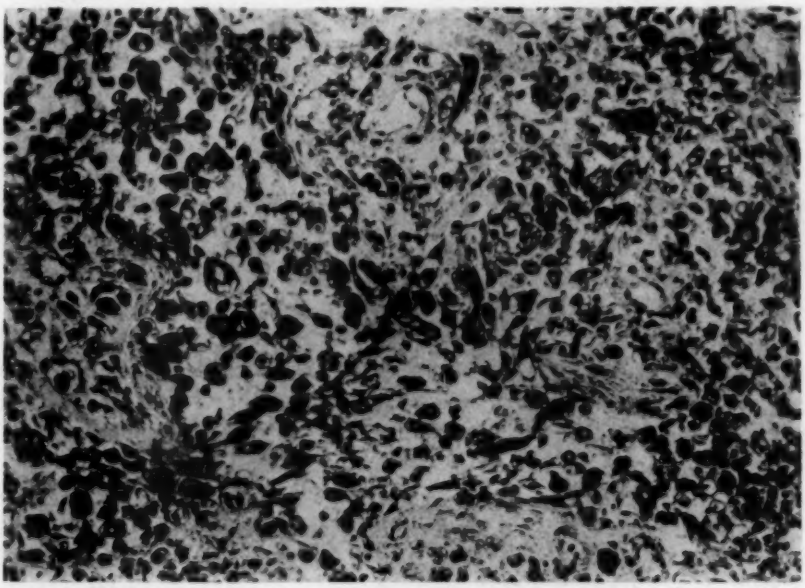

Fig. 4.—Tumor metastases in the lower lobe of the left lung. A number of large protoplasmic masses are included; × 151.

of considerable variation in contour it seemed probable that these cells had third dimensions unequal to the other two and tended to be cylindric. This belief was strengthened by the presence of elongated protoplasmic masses with fine longitudinal striae, wider at one end than at the other, the broad end enclosing the nucleus. A layer of cells was usually in direct continuity with the vascular septums, some closely approximated with a broad attachment to the stroma or extending away like a pallisade at right angles, the nucleus at the distal end of an elongated cell, and the proximal portion like a pedicle, narrow at the base (fig. 2). Among these cells that were closely applied to the fibrous septums were several cells, 40 microns and more in length, elongated and spindle-shaped, like segments of developing muscle fibers (fig. 4) with delicate longitudinal fibrils and cross-barred striations just like the bands of skeletal muscle fibers. There was little, if any, appreciable fibrous stroma between the cells. In addition, there were

cells with a short tapering end like a "comet," the nucleus at the broad end; round cells with centrally placed vesicular nuclei, having in their cystoplasm concentrically arranged fibrils with segmented granules like cross striations and, in the nucleus, many small threadlike filaments; and large oval acidophilic masses of cytoplasm with a marginal border like a sarcolemma and many small irregular vesicular nuclei arranged peripherally. Among the septums were isolated fibrils and small bundles of fibrils like a delicate tracing of fine lines with alternating light and dark segments. In the tissues from the left thigh and leg, especially where edema was marked, most of the cytoplasm and nuclear structures of certain cells had disappeared, leaving only narrow rings, structures which corresponded in a general way to the sarcolemma of skeletal muscle fibers. Tissues from the primary tumor and from many of the metastases fixed in absolute alcohol were stained for glycogen. All of these tumor tissues contained many cells with glycogen granules.

The microscopic examination of the spleen, liver, kidney, myocardium, pancreas, esophagus, aorta, testes, epididymides, accessory splenic nodule, gallbladder, stomach, small bowel and trachea disclosed no additional features of interest. The nodular masses in the right leaf of the diaphragm were tumor tissue with a predominance of the smaller variety of cells like large round cells, but they included also a number of larger cells with acidophilic cytoplasm. The bone tissues of the ramus superior of the left os pubis were extensively destroyed by tumor.

COMMENT

The tumor described originated, no doubt, in skeletal muscle of the left leg. This conclusion follows because in all metastatic tissues removed during life or examined post mortem, cells were found which were primitive or abortive muscle structure, containing acidophilic cytoplasm, an ectoplasm resembling a sarcolemma, one or more vesicular nuclei, and concentric fibrils with alternating light and dark bands or protoplasmic prolongations having longitudinal fibrils and cross-striations like the light and dark bands of skeletal muscle. The cells in all of the areas of metastasis examined contained large quantities of glycogen.

INGUINAL LYMPHADENITIS

WITH SPECIAL REFERENCE TO THE GROUP KNOWN AS CLIMATIC BUBO *

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About two years ago there was received at the Hygienic Laboratory of the U. S. Public Health Service a lymph gland which revealed a picture unlike any of the usual adenopathies, but resembling closely the picture for climatic bubo described in the literature. Since that time a number of similar cases have been studied, and also a number of histologically dissimilar cases of adenitis diagnosed clinically as climatic bubo. As microscopic descriptions of the condition have been few, and as some of these cases showed a close correspondence to the microscopic changes described in cases of climatic bubo, they are deemed worthy of reporting.

Letulle and Nattan-Larrier [1] studied a case of bubo of some months' duration in a young Costa Rican. This gland showed some normal follicles, and a much diffuse, disordered area in which the follicles and sinuses had disappeared and in which, in the meshes of the reticular tissue, lymphocytes and an excessive proportion of plasma cells were seen, with here and there plasma cell nodules. The gland also showed distention of the blood vessels with margination and emigration of polymorphonuclear leukocytes; foci of necrosis with pyknosis and karyorrhexis, hyalinization and increased vividness of staining of the cytoplasm; and numerous polymorphonuclear leukocytes and other phagocytes nearby.

Foci of suppuration were also seen showing disorganized tissue distended with polymorphonuclear leukocytes, some of which were partially disintegrated.

Recent and old hemorrhagic foci were seen, the latter with hemosiderin. The periglandular vessels showed perivascular mesovascular and endovascular infiltration with round cells.

Thickening and general increase of fibrous tissue were observed, with infiltration of the interstices with plasma cells and lymphocytes. There were intracellular inclusions in plasma cells near the necrotic foci. These were ovoid, measuring from 4 to 5 microns by 3 microns,

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* From the Hygienic Laboratory, U. S. Public Health Service.

1. Letulle, M., and Nattan-Larrier, L.: Bull. Soc. path. exot. **3**:755, 1910.

and containing two unequal chromatic granules. These inclusions were considered as possibly nuclear débris, possibly parasitic. None of the usual bacterial stains revealed recognizable organisms.

Müller and Justi [2] described the pathologic changes in two cases. The first presented several large, tense glands with thickened capsules. The cut surface was light grayish red, with several irregularly disposed necrotic foci, some with abscess cavities. The periglandular fatty tissue showed dilated vessels and some swollen septums infiltrated with large cells with pale vesicular nuclei containing acidophilic nucleoli and granular or vacuolated cytoplasm. The cells formed a reticulum with their prolonged processes. In the meshes were seen numerous lymphocytes, polymorphonuclears and red cells. Numerous mitoses were present. Some fibrin was found. The gland capsule showed young fibroblasts, numerous erythrocytes, lymphocytes and plasma cells.

The gland substance showed many blood vessels. The capillaries especially showed endothelial swelling and proliferation, and near the necrotic foci hyaline thrombi. The dilated vessels contained neutrophil leukocytes in the lumen and in their walls. The normal gland structure was obliterated.

In some areas there was marked proliferation of the reticulum with large nuclei and numerous mitoses. In the meshes were lymphocytes and plasma cells, the latter with from one to six nuclei, also cells with large nuclei and narrow cytoplasm (endothelium cells) and numerous transitional forms between these and the plasma cells. Mitoses were frequent in all these cells. In some areas the lymphocytes predominated, in others the plasma cells. In some places there were numerous erythrocytes.

Near the necrosis there was proliferation of the reticulum cells and endothelium cells to form new connective tissue, the cells taking on the appearance of young fibroblasts. Here the meshes were narrower and contained lymphoid cells in smaller numbers.

The necrotic foci were either sharply demarcated or set off by a marginal zone in which the nuclei of the reticular and endothelial cells persisted, often elongate like the palisade cells in a gumma. Polymorphonuclears, lymphocytes and plasma cells were also found in this zone. In the necrotic areas proper, the reticulum might or might not be recognizable. Nuclear fragments of all sizes were seen, as well as cytoplasmic débris. Necrotic leukocytes were seen. Here and there was evidence of calcification.

There was widespread deposit of either hyalin or fibrin, especially about capillaries and near the necrotic foci.

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2. Müller, O., and Justi, K.: Beihsfte z. Arch. f. Schiffs- u. Tropen-Hyg. **18**:857, 1914.

A few bacteria were found in one section in the margin of an area of necrosis. These were short, fat, club-shape rods, mostly extracellular, but occasionally in an oval vacuole in a reticulum cell. The free bacteria stained violet with Giemsa.

Their second case showed greatly hypertrophied germinal centers appearing almost like tubercles under low magnification. There were close packed vesicular nuclei. Many mitoses were present. Some cells showed beginning karyolysis, others complete fragmentation of the nucleus. The cytoplasm of the necrotic cells coalesced into a finely granular mass containing nuclear fragments. A few polymorphonuclear leukocytes were found about these foci of necrosis. Bacteria resembling those seen in the first case were also seen in this.

Stefko [3] described briefly two cases in which blood cultures produced *Staphylococcus aureus*. The first showed an acute lymphadenitis, the second a chronic fibrous lymphadenitis with numerous plasmatocytes, fibroblasts and abundant connective tissue. This case showed also *Plasmodium malariae* in the blood.

Castellani and Chalmers [4] stated that the capsule of the gland is much thickened, interstitial tissue is abundant, there is great proliferation of lymphocytes, hemorrhagic foci occur here and there and numerous plasma cells are present.

Whitmore's [5] paper on climatic bubo contains brief histologic descriptions of four of his cases:

> CASE 1.—Sections show a thickened capsule and marked fibrosis throughout the tissue. The germinal centers are well defined and enlarged. The medullary sinuses and blood vessels are distinctly dilated and full of fluid. Numerous areas of leukocytic infiltration are seen, being especially evident in the cortex. In many of the germinal centers small abscess formation has developed.
>
> CASE 2.—Sections show the entire gland to be the seat of acute inflammatory reaction associated with vast areas of necrosis and localized abscess formation.
>
> CASE 9.—Chronic inflammation and abscess formation; no evidence of specific or tuberculous infection.
>
> CASE 10.— . . . sections showed marked proliferation of germinal centers in peripheral parts of glands, with multiple necrotic foci in central parts; marked periglandular inflammation with round cell infiltration. . . .

Hanschell [6] found no constant histologic differences distinguishing the morbid changes in climatic bubo from those seen in genital scabies or ulcus molle.

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3. Stefko, W.: Bull. Soc. path. exot. **10**:724, 1917.

4. Castellani and Chalmers: Manual of Tropical Medicine, New York, William Wood & Company, 1919.

5. Whitmore, W. H.: U. S. Nav. M. Bull. **25**:89, 1927

6. Hanschell, H. M.: Lancet **211**:276, 1926.

Günther [7] described gross capsular thickening and multiple small abscesses; histologically necrosis bordered by radially disposed epithelioid cells in a broad zone, reactive proliferation of the reticulum, fibrinous inflammation; in earlier stages, a thickening of the fibers of the reticulum, which were broken down in and near the necroses; later diffuse conversion of the reticulum into collagen and resulting diffuse fibrosis. The cell inclusions described earlier by this author he now considered as probably nuclear or cellular débris rather than parasitic.

Uribe [8] described the characteristic infiltration with large numbers of plasma cells; formation of granulomas with epithelioid margins and amorphous centers; stellate abscesses with similar walls and contents of polymorphonuclear leukocytes and large mononuclear cells; obiliterating endarteritis and hemorrhages, both in capsule and in parenchyma. Giant cells of undescribed type, occurred in the infiltrated tissues. Some glands showed simple hyperplasia and congestion, with occasional small hemorrhages.

Sections from the material remaining on hand at the Hygienic Laboratory from Barber and Coogle's [9] case show marked hyperplasia and proliferation of the reticulo-endothelium, diffuse infiltration of the rest of the gland pulp by small lymphocytes, a densely fibrous capsule, with only a few thickened vessels and an occasional patch of infiltration with round cells, an entire absence of focal hemorrhage or necroses and absence of areas of infiltration with plasma cells. This material does not, as Hansmann [10] said, resemble the nontuberculous granulomatous lymphadenitis described by him; neither does it, in my opinion, resemble that in the cases described by Müller and Justi.

The other references that were available contained either nothing bearing on the microscopic changes or citations only.

REPORT OF CASES

Case 1.—G. E., aged 39, a white marine fireman, on July 9, 1926, while in Galveston, Texas, struck himself in the left groin with an iron bar. There was an excruciating pain at once, and soon after a swelling in the left groin, which remained painful.

This was the patient's first and only excursion into the tropics, all previous service having been on the Great Lakes. He was admitted to the Marine Hospital at Ellis Island, New York, on July 22. There was no evidence or history of venereal disease. He had a temperature of from 99 to 100 F. for the first week in the hospital. Adenectomy was done on July 30. Grossly, the glands were friable and not encapsulated. The cultures gave no growth.

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7. Günther, Reinhard: Arch. f. Schiffs- u. Tropen-Hyg. **29**:546, 1925.

8. De Bellard, E. P., and Uribe, Cesar: Gac. méd. de Carácas **32**:100, 1926 (cf. pp. 106-108, particularly); de Bellard, E. P.: J. Trop. Med. **29**:103, 1926.

9. Barber and Coogle: U. S. Pub. Health Rep. **42**:1306, 1927.

10. Hansmann, G. H.: Surg. Gynec. Obst. **39**:72 (July) 1924.

Histologically, there were diffuse fibrosis and infiltration with plasma cells, foci of necrosis, small abscesses, small hemorrhages and well marked periadenitis.

The areas of fibrosis varied from dense fibrous tissue to loose connective tissue with many large fibroblasts having large, oval leptochromatic nuclei and in the interstices numerous plasma cells and a few lymphocytes. Among them were large, deeply staining syncytial masses with sharply rounded margins and from two to five nuclei the chromatin of which lay in radially disposed coarse blocks and about the periphery. In one instance, a typical plasma cell was in contact and apparently partly fused with such a syncytium. Occasional plasma cells were in mitosis.

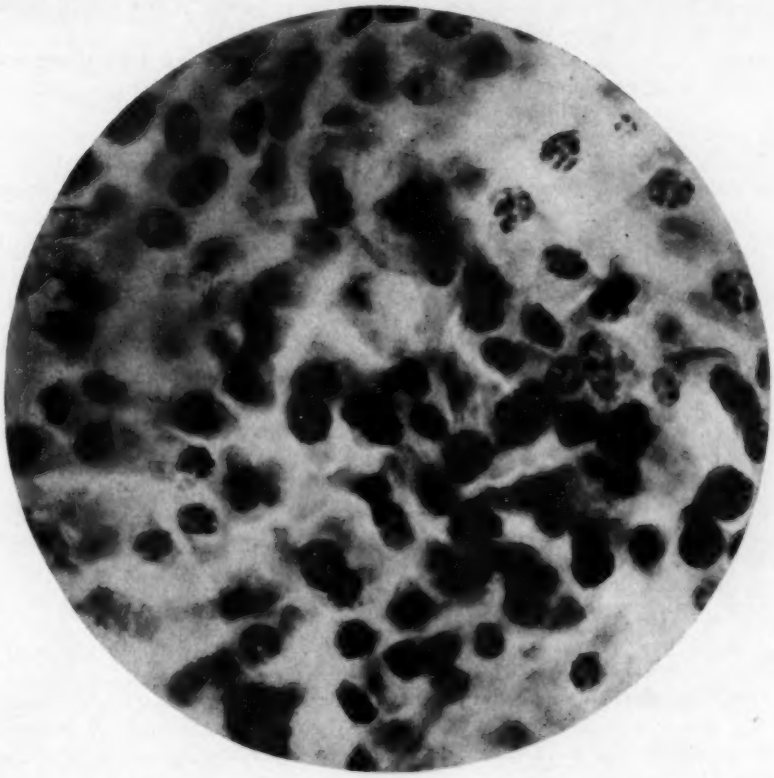

Fig. 1.—A plasma cell nodule in case 1. Hematoxylin eosin. Zeiss 60X. 1.4 N. A. Homal IV. 1,000 diameters, reduced in reproduction two-thirds.

The focal lesions consisted of large, swollen, oxyphil, poorly defined reticulum cells with well stained nuclei. In the centers of such nodular lesions, one found pyknotic nuclei and nuclear fragments either alone or with greater or less numbers of polymorphonuclear leukocytes, many of which showed disintegration and nuclear fragmentation.

About the margins of these focal lesions were found lymphocytes and plasma cells with pyknotic nuclei, considerable numbers of polymorphonuclear leukocytes and sometimes nodular accumulations of small plasma cells.

The hemorrhages were of variable age, some showing well formed red cells in the tissue adjacent to a dilated capillary; others, indistinct and malformed red

cells and many yellowish-brown pigment granules free and filling the cytoplasm of cells, some of which possessed the vesicular leptochromatic nuclei of the macrophages, others the characteristic heavily stained cartwheel nuclei of the plasma cells.

Some of the capillaries were dilated, showing margination and emigration of leukocytes. Others near by were small and contained few leukocytes. The margination and emigration were apparently not related to the nearness of foci of necrosis or abscesses.

Parts of the tissue showed normal germinal centers. Other areas resembling germinal centers showed nuclear pyknosis and fragmentation in the center, occasional polymorphonuclear leukocytes and, near the periphery, a few typical plasma cells among the lymphocytes.

In places, the capsule and, to a less extent, the surrounding fatty tissue were infiltrated with lymphocytes and plasma cells.

Case 2.—S. M., aged 21, a negro seaman (scaler), entered the Marine Hospital at Norfolk on Feb. 26, 1927, with swollen, slightly painful inguinal glands, about three days after the onset of the symptoms. The temperature ranged around 101 F. The swelling increased. On March 7, the left side was incised and drained. The fever persisted, and the glands continued to enlarge. On March 17, the left inguinal glands were excised. Following excision there was free drainage, with prompt subsidence of the fever and clinical improvement. The condition on the right side subsided without surgical intervention.

The blood count on March 31 showed a moderate anemia (3,280,000) and a white cell count of 9,000 with relative lymphocytosis (49 per cent small, 2 per cent large lymphocytes). Cultures and smears from the wound, taken about March 31, showed gram-positive cocci and gram-negative extracellular and intracellular diplococci. There were no Donovan bodies.

Histologically, the glands removed on March 17 showed foci of necrosis, with or without polymorphonuclear infiltration, hemorrhages, areas of coagulated edema, areas of infiltration with plasma cells and of proliferation of fibroblasts and early fibrosis, complete disappearance of germinal centers and mitoses in large lymphoblasts or reticulum cells. There was a periadenitis with hemorrhages and infiltration of the capsular tissue with plasma cells and lymphocytes.

The cultures and smears were unfortunately not made until two weeks after the second operation, and their significance seems at least doubtful.

Clinically, there was no evidence of gonorrhea. The patient had had a chancre of the glans over a year previously. The etiology was considered uncertain, although the postoperative bacteriologic observations might indicate a gonorrheal origin.

Case 3.—A. J., aged 25, a white seaman, had had gonorrhea in 1920, and "syphilis" with a course of "five doses of arsphenamine" six months previous to the examination reported here. The patient had spent fifteen days at St. Vincents, Canary Islands, during the first part of October, 1926. He had observed, while there, a small ulcer appearing on the penis on the day following sexual intercourse. Seven days later, he noticed a swelling of the inguinal glands. He entered the U. S. Marine Hospital at Norfolk on November 13 with a soft and fluctuating bubo, which was opened on the fifteenth day. The mass drained pus, but continued to enlarge. It was removed on November 22.

The Wassermann reaction was negative. There was no evidence of venereal disease.

Histologically, an entire loss of normal structure was noted, with suppression of germinal centers and sinuses. There were large areas of loosely packed plasma cells with excentric, dense, round cartwheel nuclei and broad basophilic cytoplasm. Some of these possessed two or more nuclei. There were other areas of plasma cells mingled with fibroblasts and fibrous tissue. Foci of necrosis were present; some were filled with polymorphonuclear leukocytes and possessed only a narrow zone of fibroblasts at the margin, while others were older with broken down, amorphous contents and a broad zone of irregularly interlacing fibroblasts at the margin.

The foci of necrosis were of variable size and form. There were other areas in which the cells were mostly lymphocytes with a few hyperplastic reticulum cells. There were a few small areas of hemorrhage in the gland substance.

The capsule showed areas of infiltration with lymphocytes and plasma cells and of hemorrhage. One small gland showed lymphoid hyperplasia only.

CASE 4.—F. M., aged 26, white, an oiler and seaman, single, had had gonorrhea in 1924. He had never been in the tropics or in any ocean port. He had lived in Cleveland for four months prior to the examination reported here.

The present illness had begun during the course of frequent and promiscuous intercourse with negro prostitutes during the few months just prior to admission to the hospital. Pain and a slight swelling in the left inguinal region were first noticed on March 20, 1927. The patient entered the U. S. Marine Hospital at Cleveland on March 28. Physical examination disclosed nothing abnormal, except the moderately tender, firm swelling about the size of a walnut in the left inguinal region and a large, moderately tender, slightly indurated prostate. The prostatic secretion contained pus cells, but no gonococci. The urine showed pus, mucus and a small amount of albumin. The Wassermann reaction was negative. The blood picture on March 30 was: red cells, 5,150,000; hemoglobin, 75 per cent; white cells, 12,100; neutrophils, 79; lymphocytes, 11; large mononuclears, 2; transitionals, 7, and eosinophils, 1 per cent.

Under local treatment, the mass first subsided, then swelled and softened. Incision and drainage were done on April 8. Culture showed no growth and smears no organisms. The glands continued to be large and indurated, draining but little. Excision was done on April 18. After a brief febrile reaction, the temperature subsided to normal, and the wound granulated and healed. On May 2, the blood picture was: red cells, 4,050,000; hemoglobin, 80 per cent; white cells, 11,830; neutrophils, 60; lymphocytes, 24; large mononuclears, 10; transitionals, 4, and eosinophils, 2. Clinically, the condition corresponded to that in climatic bubo as described in Stitt's "Manual of Tropical Medicine."

Histologically, almost complete suppression of the normal structure was observed, germinal centers being recognized in only one node. There were small foci of necrosis with polymorphonuclear leukocytes in the centers and borders of irregularly disposed epithelioid cells. There were numerous small hemorrhages. Extensive areas of infiltration with plasma cells appeared, some of which possessed two or three nuclei. Small areas of coagulated edema were scattered through the gland substance. Areas of more or less dense fibrosis infiltrated with plasma cells were seen. The gland capsule showed extensive fibrosis of varying density, infiltrated with plasma cells, lymphocytes, plasmacytoid lymphocytes and histioid wandering cells, more especially in the less fibrotic areas. Young fibroblasts were numerous also. An area of hemorrhagic necrosis containing a few broken down cells and leukocytes was noted in the capsular tissue. Its margin showed partial fibrosis with lymphocytes and a few plasma cells and macrophages. Giant cells were absent. Several arterioles with organized thrombi infiltrated with lymphocytes were seen in the periglandular tissues.

CASE 5.—G. R., aged 29, a white seaman, about Feb. 11, 1927, noticed a small swelling in the left groin. This increased in size and became rather painful and tender. He entered the hospital on February 23. He offered no history of injury or of venereal disease. About January 11, he had had intercourse with a negro woman in Port Arthur, Texas. On admission, there was no evidence of venereal disease or of other local cause for lymphadenitis.

The clinical diagnosis was climatic bubo. Adenectomy was performed on February 24. The glands were enlarged, with necrotic centers and periglandular involvement.

Histologically, the lymph gland structure was largely obliterated, few germinal centers being preserved. There were numerous foci of necrosis bordered by narrow zones of swollen, ragged epithelioid cells with oxyphil cytoplasm. These foci contained cellular and nuclear débris. Many of them contained numerous polymorphonuclear leukocytes, and others swollen, vacuolated, degenerate, large mononuclear cells. There were a few small recent and older hemorrhages. There were extensive areas of infiltration of the lymphoid tissue with plasma cells. There were patches of proliferation of fibroblasts without collagen fibers. The capsule showed infiltration with lymphocytes and plasma cells.

CASE 6.—J. Z., aged 23, a white marine fireman, entered the hospital with a swelling of the left inguinal lymph glands of three weeks' duration. No lesion was found about the genitalia, anus or lower extremity to account for the lymphadenitis. The swelling had been gradual. The patient had just returned from South America and the West Indies.

The clinical diagnosis was climatic bubo. At operation on May 4, 1927, enlarged inguinal glands with central areas of necrosis were removed.

Histologically, there were multiple, irregularly shaped, small areas of necrosis with margins of epithelioid cells, some showing typical palisading, others being irregular. The contents were, in some, polymorphonuclear leukocytes, in some, leukocytes and lymphocytes; in others, amorphous products with a few nuclear fragments. There were also foci of epithelioid cells with or without central polymorphonuclear infiltration. Some parts of the gland showed diffuse interstitial fibrosis, infiltration by plasma cells and loss of normal structure with a few recent hemorrhages. Some of the plasma cells were multinuclear. One portion of the gland showed large, pale germinal centers with numerous mitotic figures and some small hemorrhages in the germinal centers.

CASE 7.—J. M., aged 32, a white seaman, for three months previous to the examination reported here, had been employed on a coastal fishing vessel. About four weeks previous, the glands in the left inguinal region began to enlarge. There was a gradual increase in size to a large, firm, tender mass measuring from 4 to 5 inches (from 10.16 to 12.7 cm.) in diameter. There was no history of venereal disease, though the patient had had intercourse with different women at intervals of from two to three weeks. Physical examination revealed only the local glandular mass, without evidence of venereal disease.

The red cells were 3,800,000; hemoglobin, 75 per cent and white cells 9,000. The differential count was not recorded. The Wassermann reaction was negative. The urine was essentially normal.

Adenectomy was done on June 8, 1927, about 11 a. m., and the material was received at the Hygienic Laboratory at 1:30 p. m. in a sterile container. Parts were at once fixed in Zenker Helly fluid. Part was used for cultures and for inoculations into animals, the results of which will be discussed later.

Histologically, only an occasional germinal center persisted. There were numerous focal lesions consisting of (*a*) small and larger interstitial hemorrhages, (*b*) small foci of necrosis with nuclear fragmentation in centers bordering direct on lymphoid tissue, (*c*) foci of epithelioid cells and large swollen mononuclear cells with oval leptochromatic nuclei, with or without a few polymorphonuclears in the center, and (*d*) areas of necrosis of irregular size and form, bordered by irregularly disposed or occasionally palisaded epithelioid cells, mingled with vacuolated macrophages and an occasional multinuclear Langhans' cell. The contents were broken-down cells and leukocytes.

Fig. 2.—Plasma cells and fibrosis in case 7: hematoxylin eosin. Zeiss 60X. 1.4 N. A. Homal IV. 900 diameters, reduced in reproduction two-thirds.

Between these were areas in which plasma cells were mixed in varying proportions with the lymphocytes, from a few up to complete replacement. Some of these possessed from two to five nuclei of the characteristic cartwheel structure. These areas were often extensive. There were a few areas of proliferating fibroblasts with a few collagen fibers mixed with plasma cells, especially about arterioles.

The periglandular tissue showed patches of infiltration mainly with plasma cells. One small node showed only small active germinal centers, reticuloendothelial hyperplasia with some degenerate, though not definitely necrotic cells of reticulum-macrophage type in the sinuses and a few small foci of infiltration with plasma cells in the pulp.

The cultures yielded an organism of the colon group, which could not be precisely identified with any of the hitherto described species. This organism was agglutinated by the patient's serum in a dilution of 1:80. Agglutination with serums of four other patients with climatic bubo was negative. Positive agglutinations in dilutions of 1:40 or over were obtained with five other serums of about 120 examined from patients suffering from various conditions. It was therefore concluded that the organism was not the specific cause of climatic bubo.

Inoculations of the fresh gland into rats, rabbits and guinea-pigs gave essentially negative results.

CASE 8.—J. G., aged 35, a sea cook, had been employed for six months prior to admission to the hospital on a Coast Guard cutter operating out of the port of New York. There had been no service in the tropics. On admission to the hospital, the patient presented a left inguinal lymphadenitis of one month's duration. There had been no genital lesion. Adenectomy was performed on Sept. 15, 1927, a fused mass of enlarged glands being found.

Histologically, there was complete loss of normal lymph gland structure, with foci of necrosis and smaller abscesses having irregular, reticulated margins, small recent and older hemorrhages, foci of edema and areas of infiltration with plasma cells, some of which possessed two or three nuclei, grading over into areas of proliferating fibroblasts mixed with plasma cells.

CASE 9.—F. M., aged 28, a negro seaman, on admission, presented a bilateral inguinal lymphadenitis of two months' duration for which no cause could be found and which was diagnosed climatic bubo clinically.

Adenectomy was done on July 16, 1928, a mass of partly necrotic glands being found on the right side, but no free pus.

Histologically, there were found, in two fragments, several rather large areas of caseous necrosis, and in all, multiple small foci of necrosis containing polymorphonuclear leukocytes and bordered by an irregular fringe of reticulo-endothelial cells, which were often swollen and degenerate. No germinal centers persisted in most of the tissue, and in the remainder, they were small and atrophic. There were considerable areas in which plasma cells and plasmacytoid lymphocytes predominated. Areas of fibrosis were present but were relatively inconspicuous. The capsule was densely fibrous with but few foci of infiltration with round cells.

CASE 10.—L. L., aged 23, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of six weeks' duration. The affected gland had previously been incised. Cultures showed staphylococci. Clinically, the case appeared to be one of climatic bubo.

Histologically, there were abscesses of varying size, filled with polymorphonuclear leukocytes, bordered by a poorly defined fringe of epithelioid cells; areas of infiltration with plasma cells; areas of proliferation of fibroblasts and fibrosis; patches of reticulo-endothelial hyperplasia and patchy infiltration of the capsule with round cells.

CASE 11.—T. W., aged 21, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of four weeks' duration. There were no lesions in the drainage area to account for the lymphadenitis. Clinically, the course of the disease was considered that of climatic bubo. At operation, the glands were enlarged and matted together.

Histologically, there was a lymphadenitis characterized by poorly walled off areas of necrosis containing cells with fragmented or karyolytic nuclei and usually polymorphonuclear leukocytes. The smaller foci of necrosis sometimes abutted directly on lymphoid tissue. The larger possessed an indefinite fringe of vacuolated, partially necrotic, stellate cells with large oval leptochromatic nuclei. The intervening gland pulp showed total disorganization of the normal structure, absence, in large part, of germinal centers, diffuse areas of proliferating fibroblasts with or without collagen fibers, inclosing between them many plasma cells and lymphocytes, and considerable areas packed with lymphocytes and a few hyper-

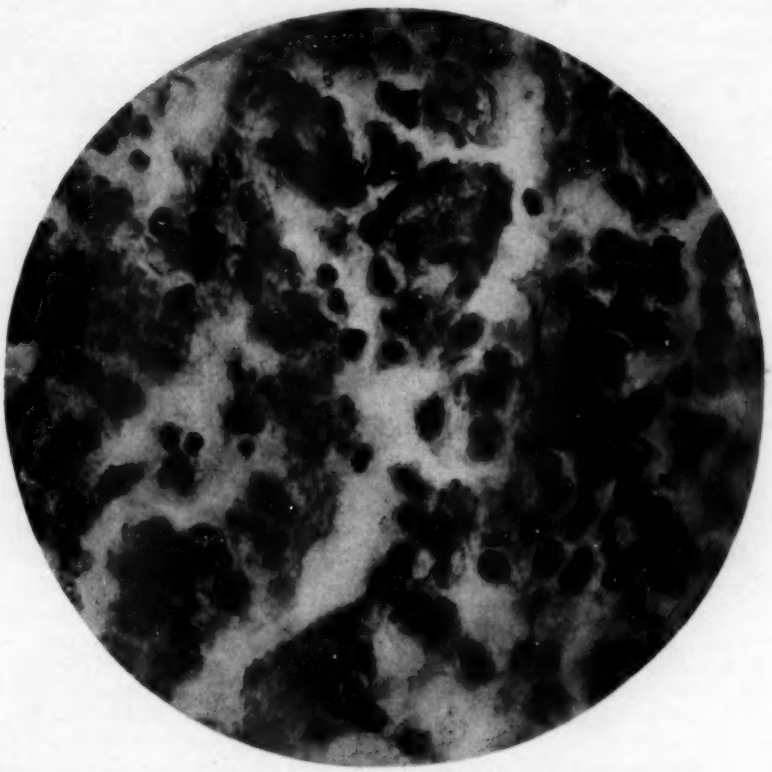

Fig. 3.—The margin of a focal lesion in case 12. Weigert fibrin. Technical details as in the legend for figure 2.

trophic reticulum cells. The capsule showed proliferation of fibroblasts, infiltration with lymphocytes and plasma cells, a few hemorrhages and some better delimited necrosis with borders of fibroblasts.

CASE 12.—T. J., aged 23, a negro seaman, said that he had been employed on a boat in Chesapeake Bay for the year previous to his admission to the hospital, and had not been farther south than Norfolk, Va. He stated that he had had no service in the tropics. He admitted frequent venereal exposure during this time, and the history given at the time of admission was that about two months previously he had noticed a slight swelling in both inguinal regions, that about

three weeks previously a sore had appeared on the "glands" and that after this the swelling in the inguinal region became more pronounced. The patient also stated that he had had a discharge for three weeks prior to admission, which was diagnosed as gonorrhea. He stated that he had had gonorrhea ten years before and a chancre in 1918, followed by antisyphilitic treatment. While the course of the adenitis and the macroscopic observations seemed to be consistent with climatic bubo, with the multiple venereal infection in this case the clinical diagnosis was rather uncertain. Clinically, however, the inguinal swelling was not the result of an infection with Ducrey's bacillus, as there was little tenderness

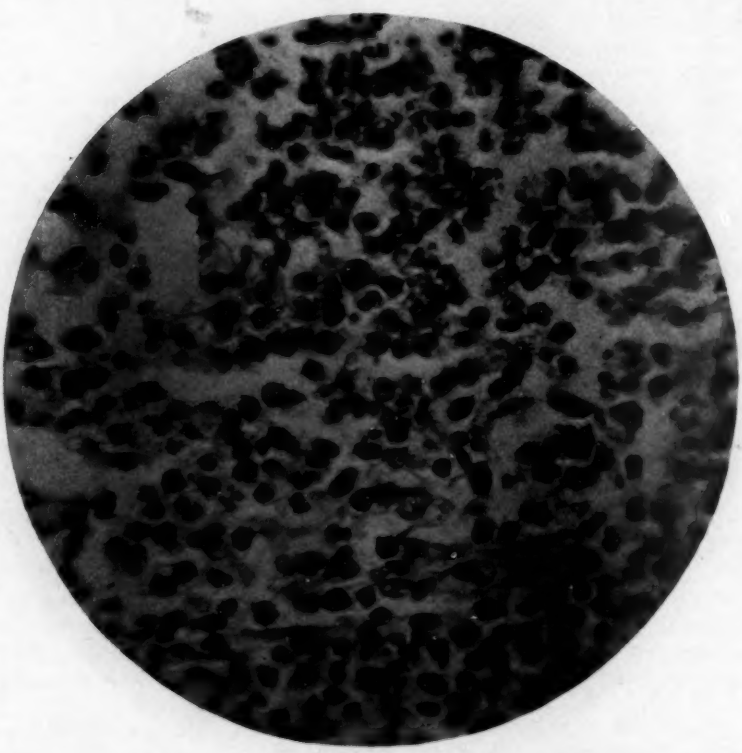

Fig. 4.—The margin of a focal lesion in case 13. Hematoxylin eosin. Zeiss 60X. 1.4 N. A. 7× Comp. oc. 500 diameters, reduced in reproduction two-thirds.

and little pain complained of at any time. Neither was it considered the result of a gonorrheal infection, as the condition was a subacute, rather painless adenopathy.

Microscopically, sections showed marked fibrosis of the periglandular tissues with patchy infiltration mainly with lymphocytes, a few plasma cells and macrophages and marked obliterative endarteritis.

In the gland tissue no germinal centers were seen. There was marked patchy interstitial fibrosis. Marked hyperplasia of the reticulo-endothelial tissue was noted in places. Some patches of recent hemorrhage and edema were seen. Multiple foci of necrosis containing pus cells, débris and coagulated serum and bordered by an irregular and rather indefinite fringe of degenerate epithelioid

cells were seen. Areas of infiltration with plasma cells, both in lymphoid tissue and in areas of proliferation of fibroblasts and fibrosis were seen. Some multinuclear plasma cells, containing two and three characteristic cartwheel nuclei, were found. Patches were seen in which there was a considerable quantity of yellowish-brown, granular pigment, free and in cells. One focal necrosis with practically no epithelioid border showed a large amount of fibrin among the pus cells and débris in the center.

CASE 13.—O. L., aged 26, a white seaman, said that he had just returned from Panama. He had signed on the SS. Feltore, which was bound for South American ports. He stated that when he arrived in Panama on the outward journey, he deserted the ship and remained in Panama approximately three weeks, coming back to Baltimore with the ship. Previous to this South American voyage he had not been going to sea. He stated that a few days after his arrival in Panama he noticed a swelling in the left groin. A few days later the right inguinal region began to swell. This swelling gradually grew worse. There was no history of any sore about the genitalia. He denied any previous venereal infection, except a soft chancre followed by inguinal adenitis in 1924. The patient admitted frequent exposure to venereal disease during his residence in Panama. There was no alleged injury as a possible causative factor. The clinical microscopic observations were consistent with climatic bubo. The only other sign of infection was carious teeth, a condition which is found in the majority of seamen.

Microscopically, sections showed a complete disorganization of the usual lymph gland structure, suppression of germinal centers, multiple irregular areas of fibrosis interspersed with and mixed with areas of infiltration with plasma cells. The latter pure areas contained often binuclear and trinuclear plasma cells, regularly numbers of plasmacytoid and ordinary lymphocytes, and often patches of hyperplastic reticulum cells. Among these types of tissue were areas of epithelioid cells centrally infiltrated with polymorphonuclears or surrounding abscesses filled with them, either well preserved or partly broken down so as to resemble caseous material. Little or no fibrin was demonstrable in the lesions.

Considerable areas of lymphocytes were also seen. There were numbers of small, fresh and older hemorrhages into the tissue.

CASE 14.—A. M., aged 40, a white seaman, had never served in the tropics. The last venereal exposure had occurred in Seattle, Wash., twenty days prior to the appearance of the lymphadenitis. After about six weeks, a mass of enlarged lymph glands with a few small foci of suppuration was removed from the right inguinal region. Recovery with firm healing was complete after a further six or seven weeks.

Histologically, one node showed simple lymphoid hyperplasia. The others showed loss of normal structure, suppression of germinal centers, areas of fibrosis and infiltration with plasma cells, areas of reticulo-endothelial proliferation and abscesses filled with polymorphonuclear leukocytes and broken down, large, round cells, and bordered by lymphoid tissue infiltrated with plasma cells. A few small hemorrhages were seen.

CASE 15.—W. H., aged 23, a white marine oiler, returned from a voyage to various ports on the east coast of South America and in the West Indies just prior to his entry into the Marine Hospital in Chelsea, Mass. The condition for which the complaint was made began on Oct. 25, 1928. The patient said that it

was brought on by heavy lifting, and that the swelling in the right groin appeared three days afterward, while he was in Buenos Aires. About the time of his admission to this hospital, on December 4, the gland broke down in two places, and pus was discharged through two sinuses, leading down to the interior of the gland. Adenectomy was done on December 11.

Histologically, sections of these lymph glands showed many small germinal centers made up of large, pale, leptochromatic cells with numerous mitotic figures and focal lesions consisting of patches of proliferated reticulum cells often centrally infiltrated with polymorphonuclear leukocytes, with or without necrosis of the reticulum cells. The margins of these areas were often infiltrated with large plasma cells with characteristic cartwheel nuclei, sometimes three or four in one cell. In other areas there was marked proliferation of the reticulo-endothelium of the sinuses, sometimes with deposition of a few collagen fibrils and a coincident infiltration with plasma cells. A few small recent hemorrhages were seen. The capsular tissue showed patchy infiltration with lymphocytes and plasma cells, often about thickened small vessels.

This case differed from some of the cases of climatic bubo in the persistence of the germinal centers, and in the relatively small amount of fibrosis and of infiltration with plasma cells. However, precisely similar focal lesions were seen in characteristic cases. Areas of infiltration with plasma cells and of hemorrhage were present and there was periadenitis.

Case 16.—E. W., aged 20, a white seaman, presented a bilateral inguinal lymphadenitis of five weeks' duration. No venereal disease was demonstrable. The patient claimed to have strained himself lifting an iron beam.

Only one small node, 1 by 0.5 by 0.5 cm., was fixed for histologic study. This showed moderate proliferation of fibroblasts and an increase of interstitial fibrous tissue, some reticulo-endothelial thickening and suppression of the germinal centers. Foci of necrosis or other well defined focal lesions were lacking.

Case 17.—H. H., aged 24, a white seaman, presented a lymphadenitis without any known or demonstrable etiologic factor. Development was slow. Adenectomy was performed two months after the onset. The glands were enlarged and necrotic, with marked periadenitis. Clinically and at operation, this was considered a case of climatic bubo.

Histologically, the glands were studded with fairly large abscesses the contents of which were partly homogenized basophilic material, partly polymorphonuclear leukocytes and fewer mononuclears. These abscesses were walled off by a somewhat irregular layer of cells resembling epithelioid cells, sometimes with definite palisading. Occasional small multinuclear giant cells occurred in this zone.

A few hyperplastic germinal centers were preserved. There were some areas of interstitial fibrosis infiltrated with lymphocytes or with plasma cells. The balance of the parenchyma of the gland was made up largely of lymphocytes, mingled with relatively few plasma cells, fairly numerous large lymphoblastic cells, a few phagocytic macrophages and hypertrophic reticulum cells.

Case 18.—L. L., aged 28, a white marine fireman, for five months prior to admission to the hospital, had been sailing to Gulf or Mexican ports. He had just returned from Gulf ports. His last intercourse was about three months prior to admission, at Tampa, Fla. He denied any soreness or irritation following the intercourse. He said that he had not had venereal infection.

On March 25, while on duty on his ship, he was lifting a heavy object and noticed a sudden pain beginning in the heel and extending up the leg into the inguinal region. There was no wound on the foot. The pain was not severe, but was more like an electric shock. The pain continued in the inguinal region, and two days later he noticed that the glands were getting large. The swelling had grown progressively larger and more painful.

Clinically, the case was considered climatic bubo. At operation, the subinguinal group of glands were enlarged and matted together. Adenectomy was done on April 6.

Paraffin sections showed numerous small foci of necrosis, bounded by epithelioid or reticulum cells in some instances showing palisading. The centers were filled with polymorphonuclear leukocytes and nuclear fragments. Areas of edema were noted. A few lymph follicles were recognizable. Swelling of the endothelia of small vessels was prominent. Plasma cells were few.

There was a well marked periadenitis with edema and infiltration with plasma cells, hemorrhages, and, in one area, dense polymorphonuclear and hemorrhagic infiltration of the fatty tissue.

CASE 19.—A. E., aged 28, a white seaman, presented an inguinal lymphadenitis of four weeks' duration the onset of which occurred apparently without any predisposing factor. No primary lesion was found. At operation, an egg-size mass of fused lymph glands was removed.

Clinically, the case was one of climatic bubo. The patient's serum failed to agglutinate *Bacterium tularense* or *B. abortus.*

Sections of the gland showed numerous focal abscesses filled with polymorphonuclear leukocytes and bordered by a usually irregular and narrow, but occasionally broad and palisaded, fringe of epithelioid cells. In the latter case, the central areas of necrosis were smaller and contained less pus. The capillaries and sinusoids showed well marked endothelial swelling. An occasional small hemorrhage was seen. There was no diffuse infiltration with plasma cells or fibrosis. Germinal centers were not recognized, but abscesses were frequent about the subcapsular zone where these are usually found.

CASE 20.—C. J., aged 23, a negro seaman, on admission to the hospital presented an inguinal lymphadenitis of one month's duration. No primary lesion was found. Cultures showed no growth and smears from the glands no bacteria. At operation, the enlarged glands were fused together.

Histologically, the lymph gland showed in some areas marked cordlike hypertrophy of the sinus endothelium, elsewhere hyperplasia of the germinal centers and elsewhere abscesses of varying sizes containing pus and cellular débris, bordered by irregularly interlaced, densely packed epithelioid cells. Nearby lymphoid tissue was infiltrated with polymorphonuclears and plasma cells. There were some patches of epithelioid cells without central necrosis.

The condition was diagnosed subacute suppurative lymphadenitis.

CASE 21.—M. L. C., aged 25, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of five weeks' duration for which no primary cause could be found. A previous incision had been made, and staphylococci were cultivated from the glands. At operation, the enlarged glands were fused together. Both grossly and clinically, the case appeared to be one of climatic bubo.

Sections showed numerous irregularly shaped foci of necrosis filled with leukocytes and necrotic débris, bordered by definitely palisaded epithelioid cells, among

which no giant cells were noted. Some metaplasia of the plasma cells of the surrounding lymphoid tissue was noted. Germinal centers were lacking. There was moderate patchy infiltration of the capsule with round cells.

The patient's serum did not agglutinate with *B. tularense.*

CASE 22.—E. S., aged 20, a white boatswain, on admission, presented an enlarged right inguinal gland of some three or four weeks' duration. The patient had had gonorrhea and chancre in 1925. Adenectomy was done on April 18, 1927.

Histologically, this lymphadenitis was characterized by partial loss of the normal structure of the gland, relatively few germinal centers persisting; by areas of recent hemorrhage and of edema; by well marked swelling of the endothelia of the smaller vessels and of the reticulo-endothelial cells of the sinuses; by an occasional small polymorphonuclear-filled abscess bordered by large cells with relatively pale vesicular nuclei, and by a well marked extensive periadenitis with swollen endothelia, dense infiltration with lymphocytes and plasma cells and an occasional fairly well formed multinuclear giant cell with peripheral nuclei.

The abscesses contained, besides polymorphonuclear leukocytes, nuclear fragments and large mononuclear cells of the macrophage type. The bulk of the tissue of the gland was made up of lymphocytes, intermingled with an occasional eosinophil and a moderate number of plasma cells. In a few foci these last predominated. Only an occasional small area of fibrosis was present.

CASE 23.—R. W. G., a white marine, was seen in the U. S. Naval Hospital in Washington under the care of Dr. White of the Naval Medical Corps, to whom I am indebted for the data and material.

Clinically, the case was one of climatic bubo. The onset occurred about June 15. At operation, August 10, the glands were apparently entirely broken down. Cultures yielded a staphylococcus and a diphtheroid, which were not further studied.

Histologically, no lymph gland tissue remained. The specimen consisted of fibrous tissue and inflammatory granulation tissue, in which were numerous plasma cells, large vacuolated macrophages, islets of lymphocytes and occasional giant cells with many peripheral nuclei. There were no definite tubercles and acid-fast bacilli were not found on extensive search.

CASE 24.—D. McP., aged 27, a white seaman, on April 25, 1927, was struck in the left groin. Acute lymphadenitis resulted, which was considered a climatic bubo. Partial adenectomy was performed shortly thereafter at Port Said, Egypt. The remaining lymph nodes became tender at intervals. Adenectomy was done on March 23, 1928. The histologic material consisted of a node measuring 1 by 0.5 inches (2.5 by 1.27 cm.).

Part of the gland showed a simple lymphoid hyperplasia of rather pronounced grade with concomitant interstitial fibrosis. The remainder showed a number of irregularly shaped caseous areas each surrounded by a wall of fibrous tissue of remarkably even thickness and suggesting strongly in the arrangement of its fiber an earlier palisading of epithelioid cells. Some of the features of these lesions suggested a late healed and inspissated suppurative lymphadenitis.

The agglutination with *B. tularense* was negative.

CASE 25.—C. J., aged 26, a white seaman, presented a climatic or tropical bubo of fourteen weeks' duration. Aerobic and anaerobic cultures showed no growth. The histologic material consisted of an inguinal lymph node 0.75 by 0.5 inches (1.87 by 1.27 cm.), with a central area of suppuration.

Histologically, the germinal centers were small, but of loose texture and made up of large, pale staining cells of the lymphoblast type. The fibrous trabeculae of the gland were generally prominent and thickened. A few small fibrosing scars containing a few plasma cells were seen. There were several small irregular abscesses with largely necrotic contents of broken down polymorphonuclear leukocytes. The walls were partly of the palisaded epithelioid cell type, partly fibrosing.

CASE 26.—A. S., aged 28, a white seaman, presented an inguinal lymphadenitis of four weeks' duration for which no primary lesion could be found. The clinical course was considered that of climatic bubo. At operation, the glands were fused together, showing necrotic centers.

Sections showed in two glands several abscesses containing partially broken-down and homogenized pus bordered by a narrow layer of fibroblasts and often considerable fibrous tissue outside these. One gland showed marked proliferation of fibroblasts and infiltration with plasma cells with recent hemorrhage in its capsule. Another showed considerable interstitial fibrosis. All but this last showed large, pale, active germinal centers and hypertrophy of the reticulo-endothelial tissue. Obliterative endarteritis was seen in inflamed areas of the capsule.

CASE 27.—J. G., aged 24, a white seaman, presented an inguinal lymphadenitis of two months' duration on which a clinical diagnosis of climatic bubo was made. At operation, a mass of inguinal glands 2.5 to 1.25 inches (6.2 by 3.1 cm.) was found. These were fused together and showed necrotic centers, but no free pus.

Histologically, this lymphadenitis showed scattered small abscesses filled with polymorphonuclear leukocytes poorly walled off and with little necrosis. There were diffuse and marked reticulo-endothelial hyperplasia, considerable interstitial fibrosis, suppression of germinal centers and capsular changes consisting of patchy infiltration with lymphocytes and polymorphonuclears and fibroblastic proliferation in the fatty tissue.

CASE 28.—L. T., aged 25, a white boatswain, had had gonorrhea six months previous to his admission to the hospital. About three weeks before entering the hospital, he was on the West Coast of Africa. Three days before admission, swelling and tenderness appeared in the left inguinal region. There was no preceding injury, and information as to venereal exposures was not obtained. Evidence of coincident venereal disease was lacking.

Histologically, there were multiple foci of necrosis bordered by irregularly disposed, partly rounded up reticulum cells, filled with leukocytes, swollen vacuolated macrophages and lymphocytes, all in varying stages of necrosis. There were also areas of proliferation of reticulo-endothelial cells. These areas sometimes showed central infiltration with polymorphonuclears. Aside from these, there was a large measure of suppression of sinus structure and germinal centers. In place of these there were areas of infiltration with plasma cells and lymphocytes and proliferation of fibroblasts with relatively little fibrosis. The gland capsule was fibrous and well defined, with a few areas of infiltration with plasma cells. A small part of the tissue showed well marked reticulo-endothelial hyperplasia and enlarged, pale germinal centers with numerous mitotic figures.

CASE 29.—I. F., aged 30, a white marine fireman, had never seen service in the tropics, having sailed only along the New England coast. He said that he had not had venereal diseases or been exposed to them. There was no antecedent injury. On admission, he presented a painful swelling in the right groin of one month's duration. Evidence of venereal disease and of local injury was lacking.

Histologically, there were extensive areas of sheetlike hyperplasia of reticulo-endothelial cells. These areas often showed central infiltration with polymorphonuclears or more or less extensive formation of abscesses. The abscesses contained principally polymorphonuclear leukocytes and a few vacuolated macrophages. Between these were more or less extensive areas of infiltration with lymphocytes and of plasma cells, often with a concomitant interstitial proliferation of fibroblasts and fibrosis. A few germinal centers persisted, showing numerous mitoses, and there were adjoining areas of reticulo-endothelial hyperplasia. Some of the abscesses were seen partly invading germinal centers. The capsule showed marked patchy infiltration with plasma cells and thickening and fibrosis of smal' vessels.

COMMENT AND SUMMARY

Histologically, these cases fall into two groups, one comprising cases 1 to 15 and 28 and 29, cases which correspond well with those described by Letulle and Nattan-Larrier, Müller and Justi, Castellani and Chalmers, and by Uribe, and the other comprising cases 16 to 27, which present no especial characteristics to differentiate them from cases of ordinary lymphadenitis.

Summarizing, the first group showed primarily foci of reticulo-endothelial proliferation with central nuclear fragmentation and necrosis, central infiltration with polymorphonuclears or definite formation of abscesses and later homogenization of the contents. In addition, small hemorrhages were frequent. Capillary thickening was common. Often the germinal centers and lymph sinuses were obliterated. Perhaps the most characteristic feature was the occurrence of considerable areas of dense infiltration with plasma cells, pure, or mixed with proliferating fibroblasts and areas of fibrosis. Regularly also there was well marked periadenitis with infiltration with plasma cells, vascular thickening and fibrosis.

Neither bacteria nor cell inclusions from the nuclear débris in the focal lesions in any of the cases of this group could be identified with certainty.

When these two histologic groups were considered in regard to certain etiologic factors, it was found that injuries were the alleged cause in two cases in one group and in three in the other. Seven of the histologically characteristic group and three of the other group had served in the tropics, while six of the first and none of the second group had not. Data as to service in the tropics were not available in thirteen cases, four in the first and nine in the second group. A possible venereal origin in the sense that the venereal contacts had preceded the origin of the bubo, not in the sense that the venereal diseases coexisted with it, was indicated in seven cases, all in the first histologic group. Trauma was not alleged and data as to possible venereal origin were not obtained in eight cases of the first group and in nine cases of the second, noncharacteristic group.

It should be here noted that the first group includes certain cases in which the clinical diagnosis of climatic bubo was not made until after the suggestion was made by the pathologist, while the second group naturally includes only cases clinically so diagnosed.

TABLE 1.—*The Relation of Service in the Tropics to the Two Histologic Groups of Cases of Inguinal Lymphadenitis*

Data on Service	Characteristic Histologically Group	Heterogenous Histologically Group	Total
Definite history of recent service	7	3	10
No service in tropics	6	0	6
No data as to service in tropics	4	9	13
Total	17	12	29

TABLE 2.—*The Relation of Certain Other Factors to the Two Histologic Groups of Cases of Inguinal Lymphadenitis*

Other Factors	Characteristic Histologically Group	Heterogenous Histologically Group	Total
Injury alleged as cause	2	3	5
Venereal exposure preceding and possibly causative of the illness	7	0	7
No history of injury and no data as to venereal contacts	8	9	17
Total	17	12	29

CONCLUSIONS

Climatic bubo is not a clinicopathologic entity. About half the cases here described were characteristic histologically and consistent with one another and with the published descriptions (1, 2, 4, 14, 15) of certain authors. The remaining cases were of the ordinary, nonspecific varieties of suppurative lymphadenitis.

Climatic bubo, while probably commoner in the tropics, is not restricted to this geographic area.

A CASE OF RHINOSPORIDIUM SEEBERI IN A RESIDENT OF THE UNITED STATES *

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AND
STELLA M. GARDNER, M.D.
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On Oct. 24, 1928, we received from Dr. M. C. Van de Venter, of Keokuk, Iowa, a tissue for histologic examination, marked "tumor of the anterior superior portion of the nasal septum."

Microscopic examination showed the tissue to be infected with *Rhinosporidium seeberi*. This organism was unfamiliar to us, but the diagnosis was suggested by Dr. Vida A. Latham and later confirmed by Prof. H. B. Ward, of the University of Illinois.

This parasite was first reported in 1900 by Seeber [1] from Buenos Aires. His patient had a large nasal polypus, which was removed with a snare, and much bleeding followed the operation. He described the parasites, which were numerous in the connective tissue of the tumor. This patient was a native of Italy, but had lived in the Argentine Republic since the age of 3 years.

In 1903, O'Kinealy [2] showed at a meeting of the Laryngological Society of London a section of a nasal polyp which had been removed in Calcutta from a native of India. Minchin and Fantham [3] studied this material and described the parasite in 1905, naming it *Rhinosporidium kinealyi*.

A number of other cases have been reported from India and from Ceylon by various observers. In fact, Wright [4] stated that this nasal infection is not uncommon in Madras.

The greater number of the rhinosporidial growths reported have been from the nasal cavity, but the parasite has been found in polypoid

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* Submitted for publication, Feb. 6, 1929.

* From the Lincoln-Gardner Laboratory.

1. Seeber, G. R.: Un nuevo esporozoario parásito del hombre dos casos encontrados en pólipos nasales, Thesis, Univ. Nac. de Buenos Aires, 1900.

2. O'Kinealy, F.: Localized Psorospermosis of the Mucous Membrane of the Septum Nasi, Proc. Laryngol. Soc. London **10**:109, 1903.

3. Minchin, E. A., and Fantham, H. B.: Rhinosporidium Kinealyi, n. g., a New Sporozoon from the Mucous Membrane of the Septum Nasi of Man, Quart. J. Micr. Sc. **49**:521, 1905.

4. Wright, J.: A Nasal Sporozoon Rhinosporidium Kinealyi, New York M. J. **86**:1149, 1907.

outgrowths of the nasopharynx, the uvula, the conjunctiva, the ear and the penis. The parasite has not been found outside the human body.

Only one case has been reported from the United States. In 1907, Wright [4] found rhinosporidium in a nasal tumor from a man who had lived his whole life near Memphis, Tenn.

Ashworth [5] between 1917 and 1921 had the unusual opportunity of studying this parasite in material from an Indian medical student, who was under observation during most of that time and who had several

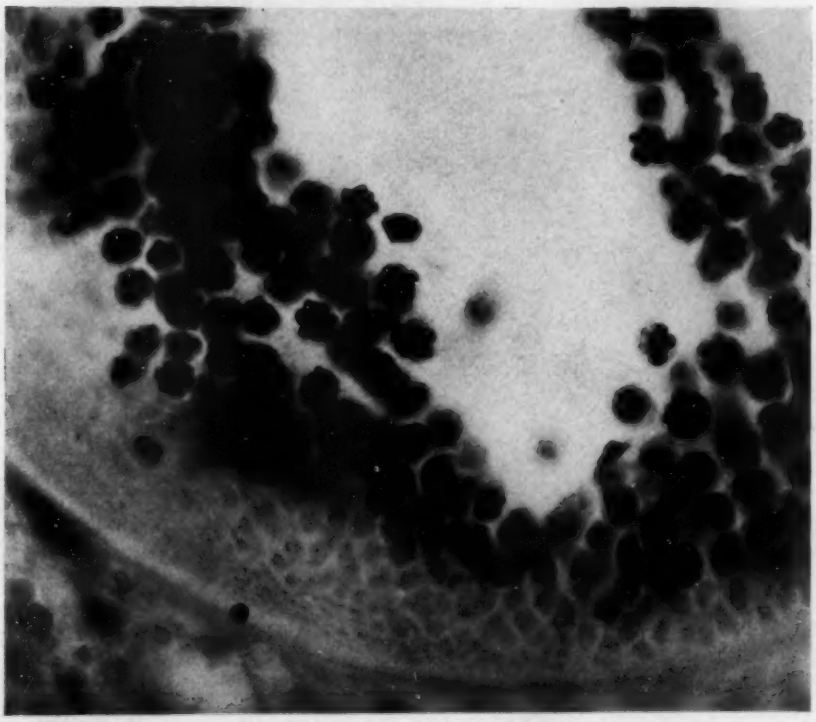

Fig. 1.—A portion of a ripe sporangium showing undeveloped spores at the periphery and ripe ones nearer the center. The ripe spores contain deeply staining spherules; × 1,000.

operations on account of the recurrence of nasal polypi. Ashworth studied the life history and development of *Rhinosporidium seeberi* in all its stages, and his account published in the "Transactions of the Royal Society of Edinburgh" in 1923 is a classic. He placed this organism under the *Phycomycetes* of the suborder *Chytridineae*, which

5. Ashworth, J. H.: On Rhinosporidium Seeberi (Wernicke, 1903), with Special Reference to Its Sporulation and Affinities, Tr. Roy. Soc. Edinburgh, 1920-1921, vol. 53, pt. 2, no. 16. Issued separately March 20, 1923.

have no mycelium. He left the exact classification undetermined, since it is unknown whether the spores develop outside the human body.

We are indebted to Prof. W. H. Taliaferro, of the University of Chicago, for the opportunity of studying some of Ashworth's slides; also for suggestions about staining and preparing our own material.

REPORT OF CASE

The history of the case in question, the tissue from which was supplied to us by Dr. M. C. Van de Venter, who removed the nasal tumor, is as follows.

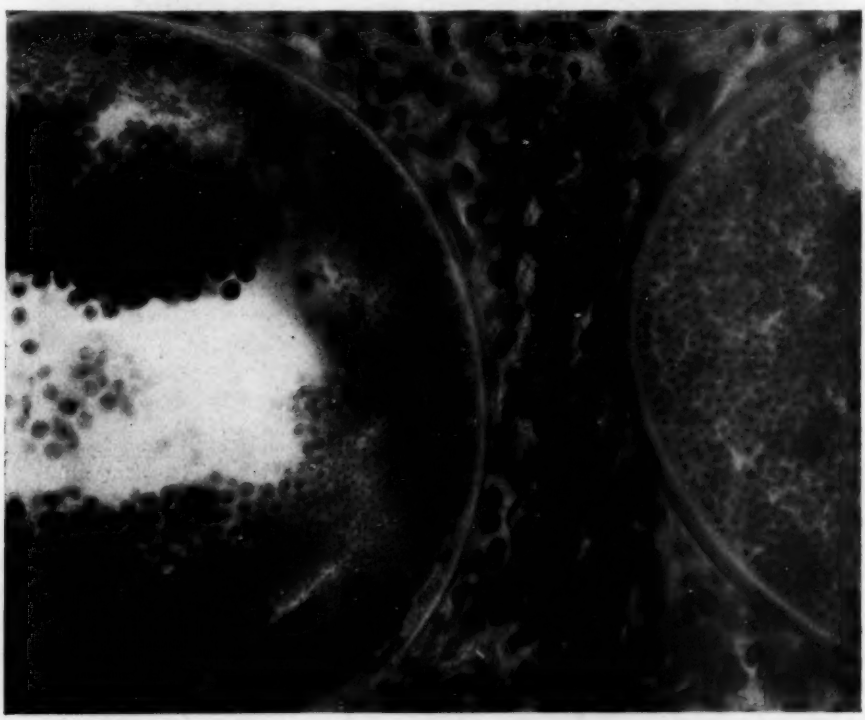

Fig. 2.—Portions of unripe and ripe sporangia; × 470.

A man, aged 40, was born in Carthage, Ill., and had lived there until he was about 17, when he spent three years in Chicago. At some later time, he lived one year in Oklahoma. In 1925, he spent nine months in Florida. He had never been outside the United States.

Thirty years before he came to Dr. Van de Venter, an operation was performed on the nose, and at that time the septum was perforated. The patient had no further trouble with the nose until twenty-two years later. Then he commenced to have a discharge and occasional bleeding.

About Oct. 20, 1928, Dr. Van de Venter removed the tumor which is described in the present paper. He stated that the patient was in good general health, that his blood gave a negative Wassermann reaction, and that healing was rapid after

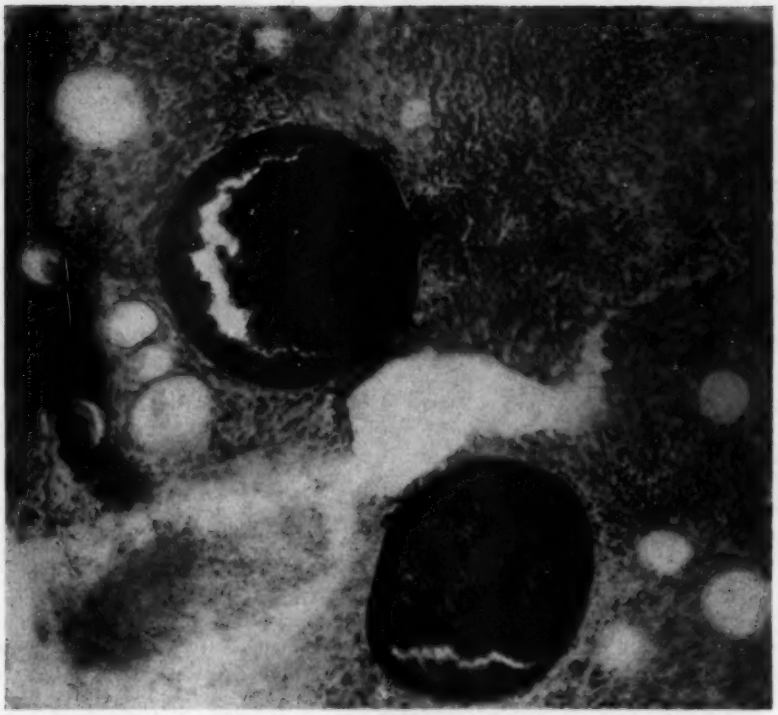

Fig. 3.—Ripe sporangia; one is discharging spores through the pore; × 125.

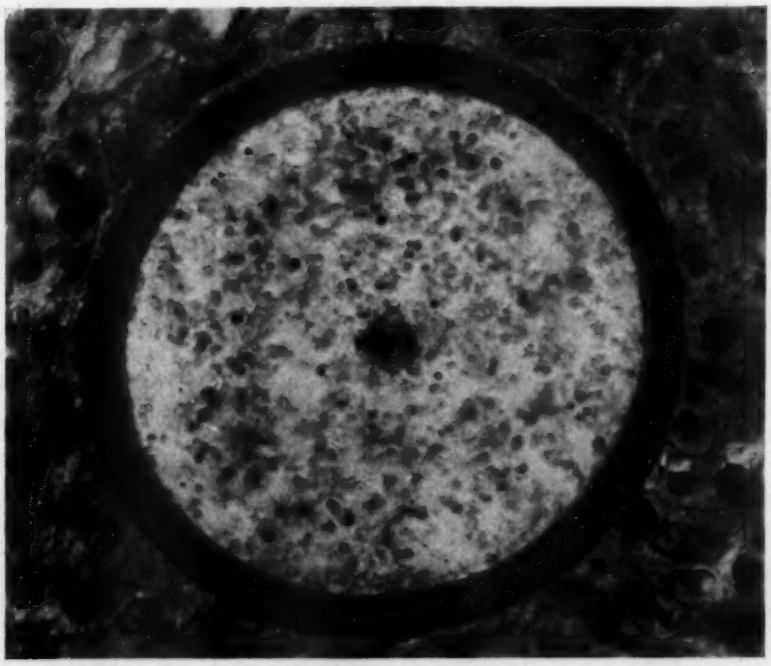

Fig. 4.—The trophic stage of the parasite, showing the thick wall, many nutrient granules and one nucleus with a large karyosome; × 900.

the operation. The patient was seen about six weeks after the operation, and there was no sign of recurrence.

The tumor when received by us was in formaldehyde. Its gross appearance was that of an ordinary nasal polypus about 1 cm. in diameter. We embedded it in celloidin and used Delafield's hematoxylin for staining. Later, in the study of cell division and nuclear structure, we used Heidenhain's iron hematoxylin.

The sections showed an inflammatory polypus rich in cell elements, such as lymphocytes, leukocytes, plasma cells and large mononucleated epithelial cells. Dipping into the polypus were many invaginations of the surface epithelium, some of which in the sections had the appearance of cysts. These pseudocysts were lined with columnar and cuboidal cells, while the surface epithelium was largely squamous, but in some areas was columnar and cuboidal. A striking feature of the histologic picture was the infiltration of the tissue by numerous polymorphonuclear leukocytes permeating the exudate of mucus, spores and blood, which often filled the pseudocysts and spread over the surface of the tumor. Venous sinuses were present and the numerous blood vessels were congested. There was also hemorrhage as shown by many red blood cells outside the blood vessels.

The most striking feature was the parasite, seen in all stages of development, the trophic stages, the sporangia and the spores. The trophic stages, which in appearance, were thick-walled spheres varying in size from 6 to 60 microns in diameter, developed from the spores, and through nuclear division grew into the sporangia. The sporangia, like the trophic stages, were spherical, but were less perfect in outline, and much larger, up to 300 microns in diameter, and had a thinner wall with a pore opening. They contained hundreds of spores and, when mature, discharged them through the pore into the surrounding tissue, or on the surface, depending on their location. The freed spores that were capable of development grew into the trophic stages, and the cycle continued.

In the ripe sporangium (figs. 1 and 2), the spores varied in appearance; those at the periphery looked like pale, uniformly staining globules about 3 microns in diameter, while those toward the center were from 7 to 9 microns in diameter, their cytoplasm being vacuolated and containing from 2 to 16 spherules. These spherules were so prominent and stained so deeply that the nucleus of the spore could hardly be seen. Earlier writers thought the spherules were reproductive sporules, but Ashworth determined that they were proteinaceous bodies and not nuclear. During the development of the young spores into the fully formed ones, the sporangium grew considerably in size, and was then the largest stage of the parasite seen in the tumor. In most of the sporangia, only a small proportion of the spores formed, and continued development to the ripe stage. Ultimately, the sporangium burst and its ripe and undeveloped spores embedded in mucus were discharged into the surrounding tissue or on the surface of the tumor to be passed in the nasal secretion (fig. 3). The compact mass of spores within the sporangium spread over a much larger area when released from the confining wall of the sporangium, so that one saw in the polypus large masses of spores embedded in mucus and intermingled with polymorphonuclear leukocytes, as well as numerous individual spores scattered among the tissue cells. Some of the pseudocysts were filled with this mixture of spores, sporules from broken-down spores, mucus and leukocytes, and often showed the collapsed sporangium wall.

The fully formed spores in the tissue after their escape from the sporangium lost their spherules, developed a thick wall and became transformed into the trophic stage. This showed a single, spherical nearly centric nucleus, with a distinct envelope and a deeply staining spherical karyosome. Its cytoplasm contained numerous granules of nutrient material, which increased in number and

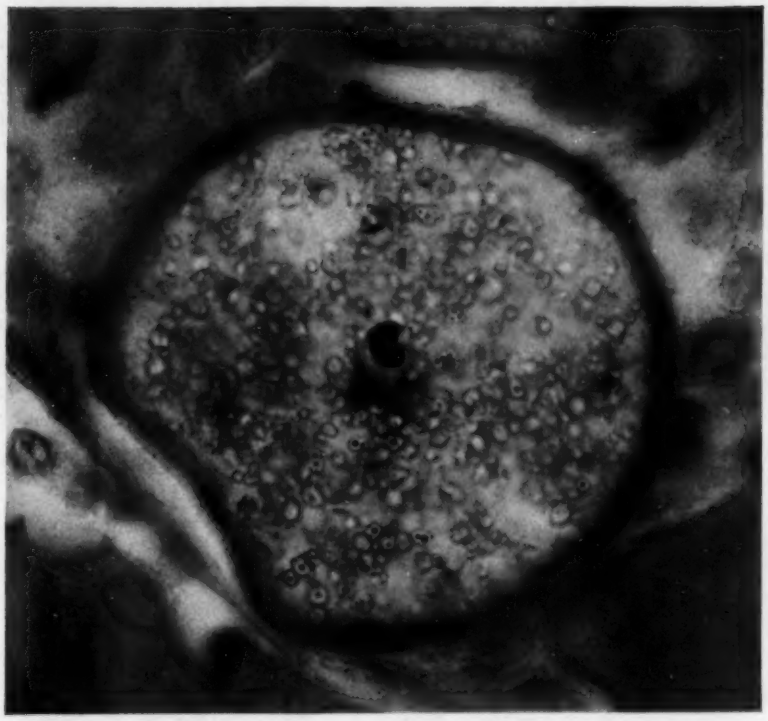

Fig. 5.—The trophic form of the parasite, showing nuclear changes preparatory to the first division; × 1,500.

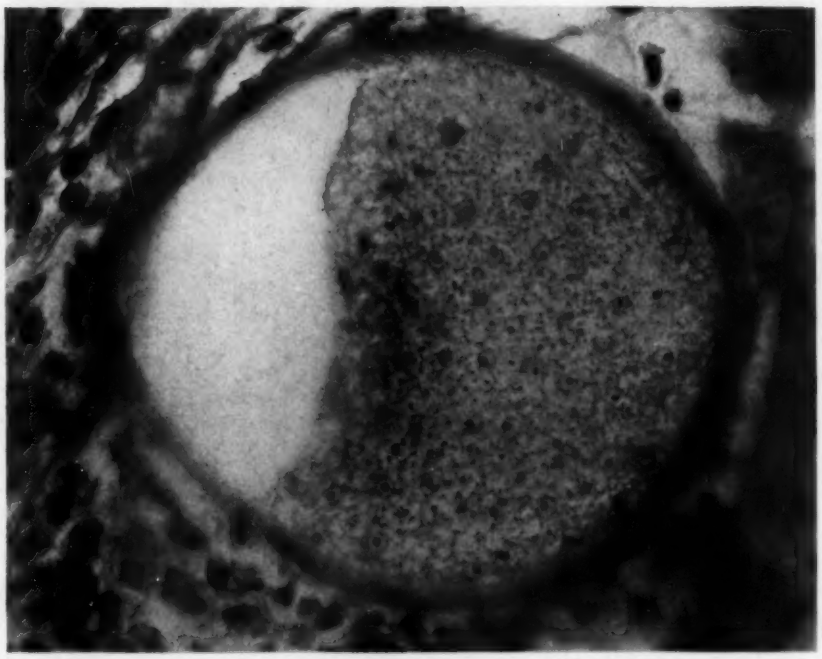

Fig. 6.—The parasite, showing many nuclei, in the resting stage; × 650.

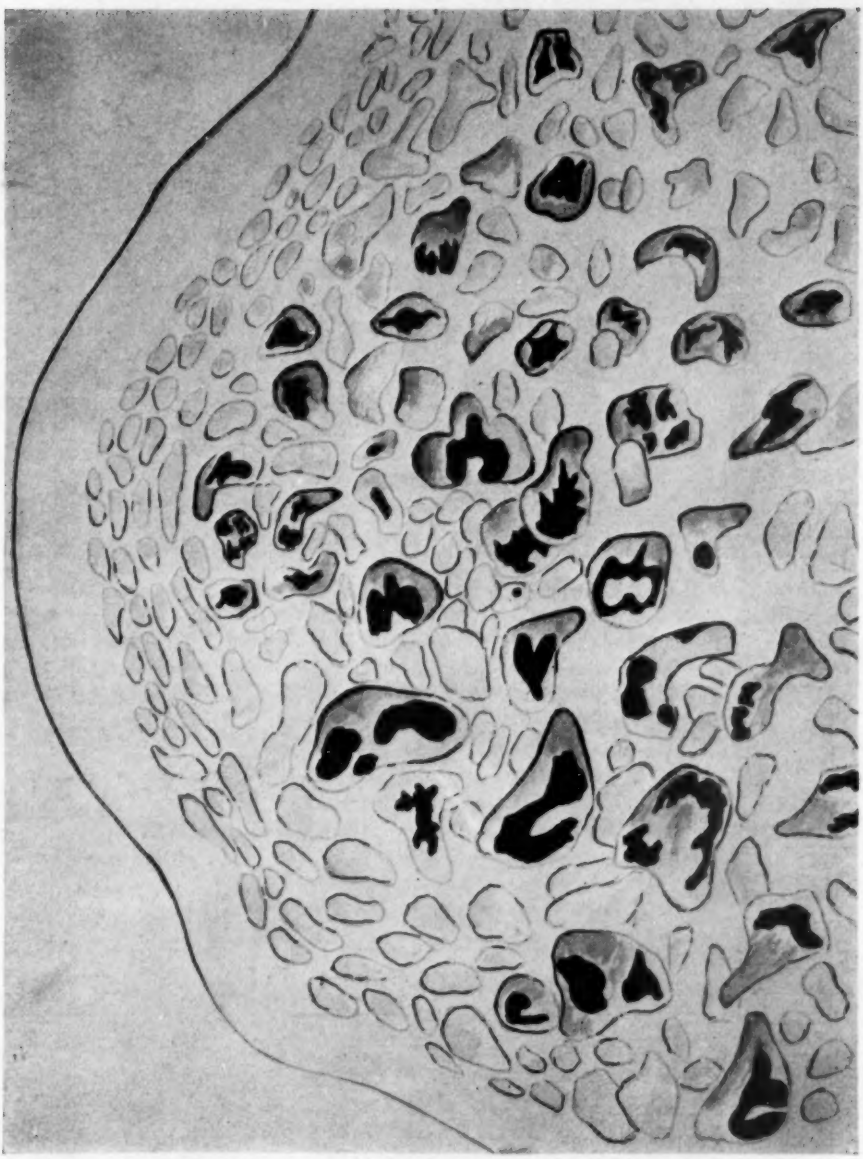

Fig. 7.—A portion of a sporangium, showing one of the latest nuclear divisions, after division of the cytoplasm (from a drawing).

size with the growth of the parasite (fig. 4). We found parasites in this stage very numerous in the tumor, but examples of parasites undergoing nuclear division were found only after considerable search.

Nuclear division began when the parasite was from about 40 to 45 microns in diameter. Ashworth in his monograph described in detail twelve nuclear divisions, which resulted in about 16,000 spores. We were unable to demonstrate in our sections the early nuclear mitoses, but found the changes in the nucleus preparatory to its division (fig. 5). Our sections also showed the stage in which many minute nuclei are in the resting condition with the cytoplasm not yet divided into cells (fig. 6).

Figure 7 shows one of the late nuclear divisions, after the contents were divided into spores. Many of these nuclei were in the dividing state. The next stage seen in our material was the sporangium with well differentiated young spores, and finally the ripe sporangium with mature spores (fig. 2).

We are reporting this case because of its rarity. So far as we have been able to find, this is the second case of *Rhinosporidium Seeberi* reported in the United States.

PRIMARY CARCINOMA OF THE LUNGS

III. HISTOGENESIS AND METAPLASIA OF BRONCHIAL EPITHELIUM*

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Until recent times, the lungs were considered to contain epithelial cells connected with three different structures: (1) the epithelium lining the bronchi; (2) the epithelial cells which form the mucous glands, and (3) the epithelium lining the pulmonary alveoli (the air sacs). Histogenetically, therefore, primary cancer of the lung was classified into three groups according to the epithelial units mentioned. Microscopically, the classification was based on the following criteria: (1) on the type of cells which were said to resemble those of the matrix, and (2) on their arrangement. Some observers have also based their genetic discrimination on the gross appearance of the tumor. Ewing,[1] who classified the tumor into the groups mentioned, stated that the combination of the clinical history, gross anatomy and histologic structure will furnish a "reasonably certain and acceptable histogenic classification." This, however, cannot be relied on. Those who have studied primary pulmonary cancer are familiar with the almost kaleidoscopic clinical manifestations of this malignant disease. The gross anatomy in this condition, as in cancer of other organs, will rarely furnish irrefutable criteria as to the particular histologic structure which gave origin to the growth. Finally, the microscopic features of a fully developed pulmonary tumor will point to its histogenesis in exceptional cases only; the morphology of the neoplastic cells varies from one tumor to another (columnar, cuboidal, spindle-shaped, so-called "oat" cells, squamous epithelial cells, basal cells), and even in the same tumor their form frequently varies from area to area. On the contrary the arrangement of the cells is rather uniform, in most instances being that of adenocarcinoma (fig. 1).

The difficulties in the genetic tracing of a primary pulmonary cancer can be illustrated by the fact that most observers are critical as to the existence of tumors having their origin in the alveolar cell, while others

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* Submitted for publication, March 15, 1929.

* From the Surgical Department of the Peter Bent Brigham Hospital.

* The preceding papers of this series have been: Primary Carcinoma of the Lungs, Arch. Int. Med. **35**:1 (Jan.) 1925; Primary Carcinoma of the Lungs: Further Study, with Particular Attention to Incidence, Diagnosis and Metastases to the Central Nervous System, ibid. **40**:340 (Sept.) 1927.

1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 851.

(Letulle [2]) do not include tumors originating in the mucous glands in their classification.

Of particular interest are blastomas said to originate from the cells lining the pulmonary alveoli (so-called respiratory epithelium).

CANCER ORIGINATING FROM CELLS LINING THE ALVEOLAR WALL

Pässler [3] (1896) was the first to give a comprehensive discussion of the question and also to review fifty-four cases of primary cancer

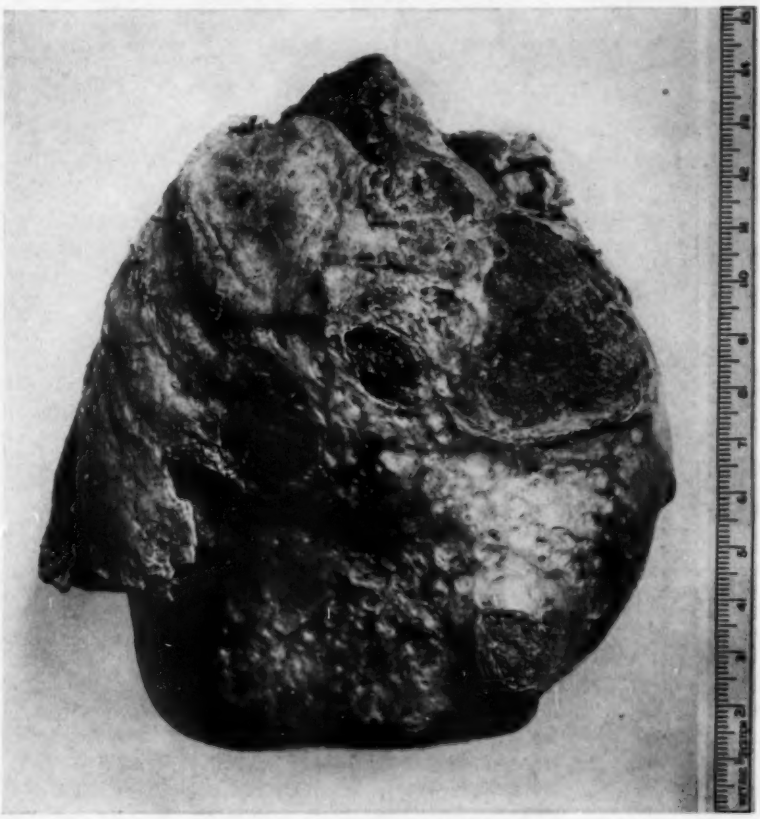

Fig. 1.—Primary bronchiogenic cancer, infiltrating type. The lung is contracted and firm. On cut surface, it resembles a pneumonic lung in the stage of red hepetization. The histologic structure of the tumor is shown in figure 3.

of the lung which he found at that period in the literature. He reached the conclusion that of this number forty-seven originated, in all

2. Letulle, M.: Le poumon, Paris, Maloine, 1924.

3. Pässler, H.: Ueber das primäre Carcinom der Lunge, Virchows Arch. f. path. Anat. **145**:191, 1896.

probability, in the bronchial mucosa; while in the others, the histogenesis could not be established. He stated, moreover, that cancers having their origin in the pulmonary parenchyma are unknown, or at least that the nonparticipation of the bronchial epithelium in these cases could not be excluded. Dömeny [4] (1902) thought that tumors made up of small and large nodules composed of small polymorphic cells forming "pearls" are of alveolar origin. Other pathologists claimed, that squamous epithelial tumors usually originate in the alveolar cells (Beitzke [5]).

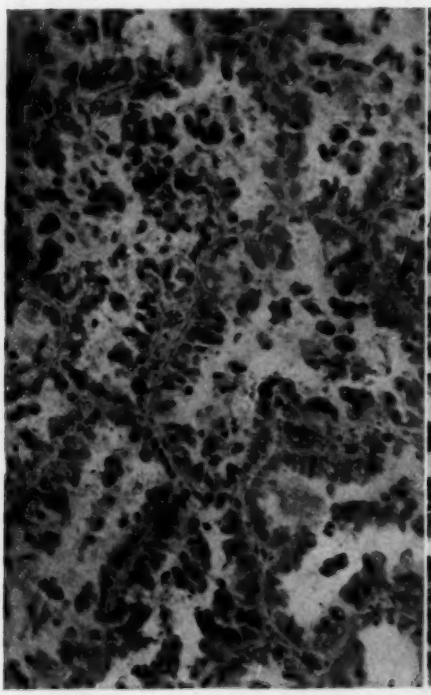

Figure 2

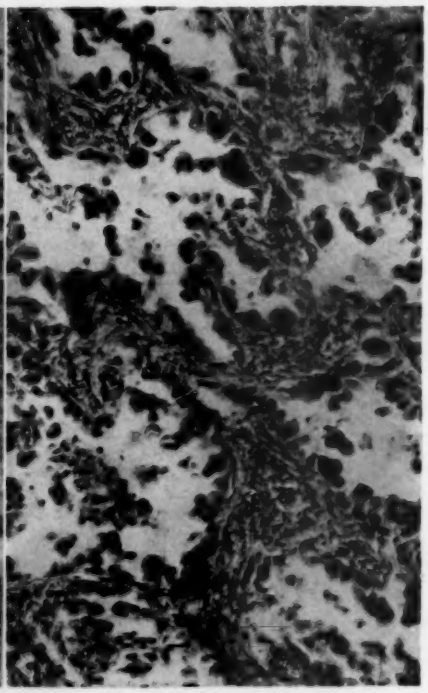

Figure 3

Fig. 2.—Primary bronchiogenic cancer. Tumor lining the wall of the alveoli.

Fig. 3.—Primary bronchiogenic cancer. The thickened alveolar wall forms papillary projections lined by neoplastic cells. The whole lung shows a marked sclerosis. The gross appearance of the lung is given in figure 1.

In 1912, Adler [6] published his monograph containing a critical review of 374 cases of primary carcinoma of the lungs. He wrote:

4. Dömeny, P.: Zur Kenntniss des Lungencarcinoms, Ztschr. f. Heilk. **23**: 407, 1902.

5. Beitzke, H.: Atmungsorgane, in Aschoff: Pathologische Anatomie, Jena, G. Fischer, 1923, vol. 2, p. 255.

6. Adler, T.: Primary Malignant Growths of the Lungs and Bronchi, New York, Paul B. Hoeber, 1912.

"It is now held that carcinoma starting from the pulmonary alveoli is extremely rare, and some go so far as to deny its existence altogether." Adler himself was of the opinion that the great majority of primary carcinomas of the lungs develop from the bronchi, and that a cancer of the lung is, strictly speaking, a bronchial carcinoma. Nevertheless, he admitted the existence of alveolar cell tumors which are built up "not of flat but of cylindrical epithelium."

My own studies in this matter have convinced me that the cells lining the air sacs do not give rise to carcinoma. Clinical and pathologic observations have led me to the conclusion [7] that these cells are not epithelial but mesenchymal in origin and consequently could not be expected to produce carcinomas. The matter may be briefly restated:

Experiments by previous workers have shown that when vital dyes in solutions are introduced into the blood stream of animals the dyes are instantaneously picked up (phagocytosed) by one variety of cells in a specific manner, being deposited in the cellular cytoplasm as fine and coarse granules. Likewise, certain lipoids (cholesterol, olive oil) introduced per os or parenterally are attacked essentially by the same large phagocytic cells—the macrophages which dispose of this substance in a way similar to that of the dye. An interesting feature in this process is the prompt morphologic changes and also the rapid proliferation of these cells.

When I made injections of oils and dyes, respectively, into the lungs of rabbits or cats by way of the trachea, the cells found alongside the wall of the air sacs responded in exactly the way the macrophage does elsewhere in the body, that is, by instantaneous proliferation and also by phagocytosis of these substances.

Further experiments [8] were conducted with the anthrax bacillus, an emulsion of which in physiologic solution of sodium chloride was injected into the animal's lungs by way of the trachea. This micro-organism was chosen because of the ease with which it can be demonstrated in tissues and, what is more important, because it is infallibly pathogenic to laboratory animals. The experiments have shown that the intratracheal route of infection causes no disease, provided the skin or the subcutaneous tissues of the animal are spared from contamination. Investigation of tissues from the rabbits so infected has disclosed that the pathogenic micro-organism is retained by the pulmonary tissue where it is destroyed within a short time after the injection. As in the previous experiments with the vital dye and with the oil, the bacillus is instantaneously attacked by the local macrophages normally harboring the pulmonary septums, and also lining the wall of the air sacs which rid the tissue of the germ by way of phagocytosis.

Investigation made on human lungs likewise shows that the air sacs are in all probability lined not by epithelial cells, but by macrophages scattered in groups along the alveolar walls. In my opinion, these cells

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7. Fried, B. M.: I. The Origin of Histiocytes (Macrophages) in the Lungs, Arch. Path. **3**:75 (May) 1927; II. The Defensive and Metabolic Apparatus of the Lungs; The Lungs and the Macrophage System, ibid. **6**:1008 (Dec.) 1928.

8. Fried, B. M.: The Infection of Rabbits with the Anthrax Bacillus by Way of the Trachea, unpublished data.

are mesenchymal in origin and therefore could not give rise to an epithelial malignant disease (fig. 4).

If one therefore excludes the alveoli as a possible source of carcinoma, there remain to be considered the mucous glands and the bronchi.

CANCER ORIGINATING FROM THE MUCOUS GLANDS

The mucous glands are structures that lie underneath the bronchial membrana basalis; indeed, being made up of epithelial cells, they are

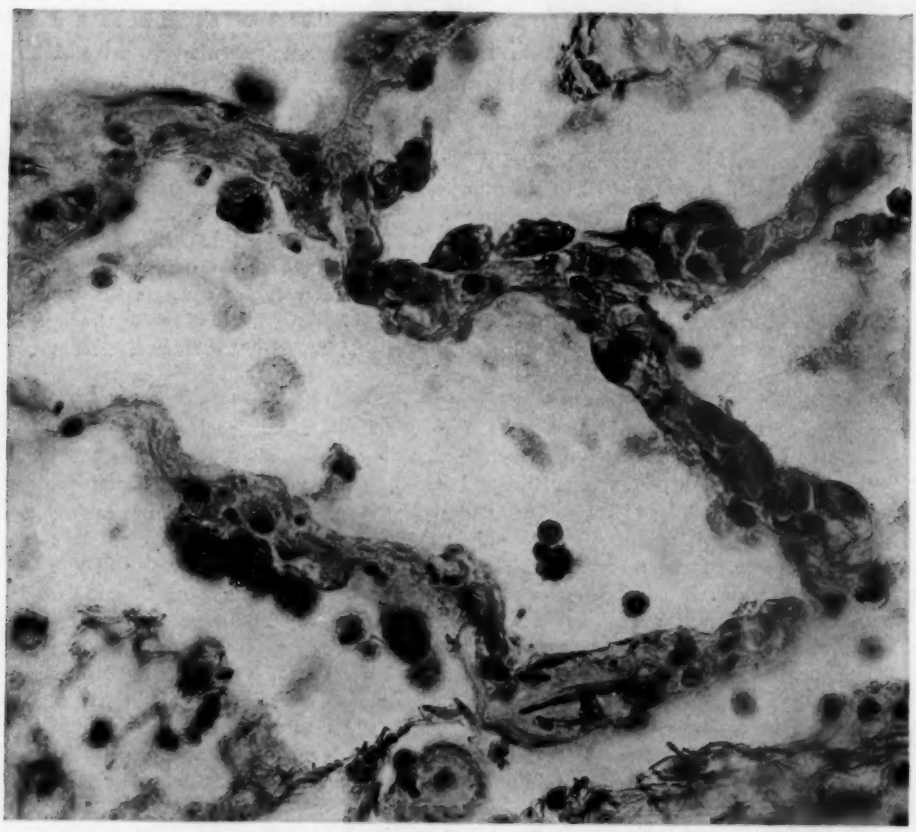

Fig. 4.—Section of human lung taken from a distended pulmonary alveolus, showing cells along the septums which to all appearances are macrophages. There is no epithelium lining the wall of the air sacs.

theoretically considered as being liable to be transformed into an epithelial malignant new growth. However, Letulle [2] did not include such a variety of tumors in his classification; moreover, the few cases reported in the literature in which the condition was believed to originate from these units are wholly unconvincing. No worker has ever observed

an early cancer of this kind, and the criteria, such as the glandular structure as well as the presence of mucus, which are claimed to be characteristic of these neoplasms, in reality distinguish a great many tumors originating from organs which normally form no mucous material.

The foregoing clinical, pathologic and experimental observations point toward the conception that primary carcinoma of the lungs is only bronchiogenic in origin (fig. 5).

REGENERATION OF BRONCHIAL EPITHELIUM AND PULMONARY CANCER

The causal and formal genesis of cancer in general and that of the lungs is a matter of dispute. Apparently a malignant disease in the

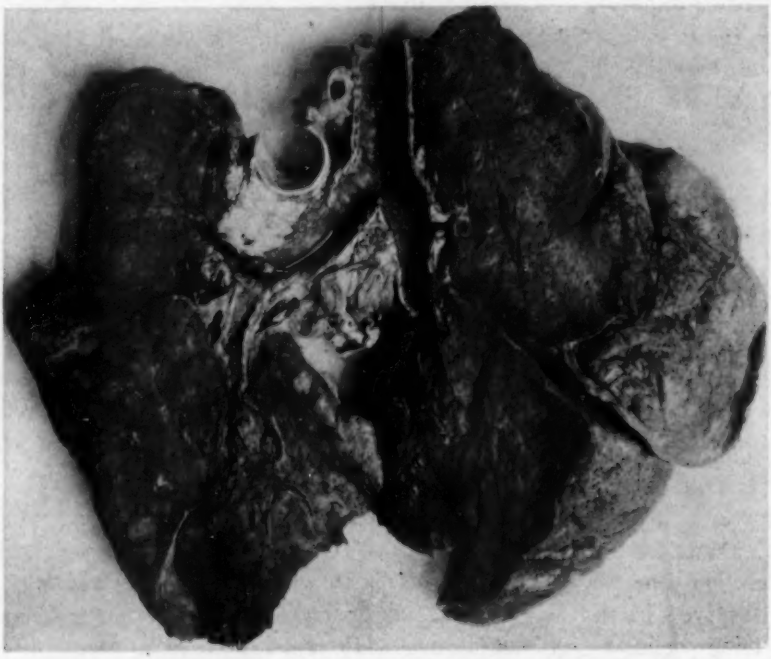

Fig. 5.—Primary bronchiogenic cancer. The cut surface of the dorsal aspect of both lungs. Tumor is seen in the first branch of the left bronchus beginning at the level of the division of the main bronchus into the two branches (indicated by arrow). The main stem of the left bronchus which enters the lower lobe, and its ventral and dorsal branches show no pathologic condition. The tumor invaded the lymph nodes. The lungs also show atelectatic areas.

lungs results from the "cancerization" of the somatic cell. This probably occurs in several ways. First, individual cells may acquire the disease, leading to their anarchic growth. Second, a local malignant condition may possibly be due to a systemic bodily imbalance of some kind. It is, moreover, probable that both conditions are required for

the development of the malady. Be that as it may, many observers are still uncertain whether a fully differentiated epithelial cell is liable to become cancerous.

It is well established that one of the factors leading to the development of a cancer is chronic inflammation, namely, irritation which causes degeneration of cells eventually followed by an excessive regeneration. However, in the lungs the columnar epithelial cells lining the bronchi have never been observed to be in a state of regeneration as evidenced by mitoses and proliferation.

Ribbert [9] was probably the first to emphasize the fact that neoplasms usually originate from cells which are not fully differentiated; other pathologists stated that in every organ there exist "embryonal centers" (physiologic centers of proliferation) which serve as a point of departure for tumors. The problem is complicated in that with the methods of observations at the present time the actual metamorphosis of a somatic cell into a malignant cell has never been observed. The skepticism is therefore based on the observation: (1) that a fully differentiated cell is generally "apotent," and (2) that regeneration, which is a forerunnner of a malignant condition, is performed in most instances by cells other than those which appear at first glance to be affected by the noxious agent. The skin is an interesting example in this respect. In the presence of damage to this structure, regeneration of the cutaneous tissue will occur by virtue of the basal cells only, which are probably postembryonic undifferentiated cells; but when these cells, too, have been damaged, a skin graft is required for the repair of the defect.

The lining of the bronchi and their divisions is made up of three different types of cells: columnar ciliated cells, goblet cells and finally basal cells, a variety of small oval cells having a narrow cytoplasm and a nucleus rich in chromatin. The last mentioned cells lie close to the basal membrane; they do not form an uninterrupted syncytium as is observed in the skin, but are irregularly scattered here and there forming cellular agglomerations. Observation reveals that in the respiratory tract the process of regeneration takes place by virtue of the just mentioned 'basal" cells, which are apparently endowed with latent developmental potentialities.

In chronic bronchopulmonary diseases accompanied by damage of the bronchial epithelium, one often notices that instead of the ciliated epithelium there appear cuboidal cells superimposed by many layers of "transitional" epithelial cells which have originated from the preexisting "basal" cells. Likewise, in chronic inflammation, these cells have

9. Ribbert, H.: Lehrbuch der allgemeinen Pathologie und der Pathologische Anatomie, Leipzig, 1905.

a tendency to invade the pulmonary alveoli lining their wall, thus giving the impression that the air sacs are normally lined by cuboidal epithelial cells. They also not infrequently invade tuberculous cavities, where they ultimately become cancerous. Similarly, in cirrhotic lungs one finds wide strands of fibrous tissue containing alveolar-like structures lined by cuboidal cells. This, too, was erroneously described as pulmonary alveoli lined by alveolar wall cells which had "reclaimed" their embryonic cuboidal aspect ("regressive metaplasia"). Askanazy described an instance in which the "basal" cells proliferated to such a degree as to invade the bronchial mucous gland. I have observed

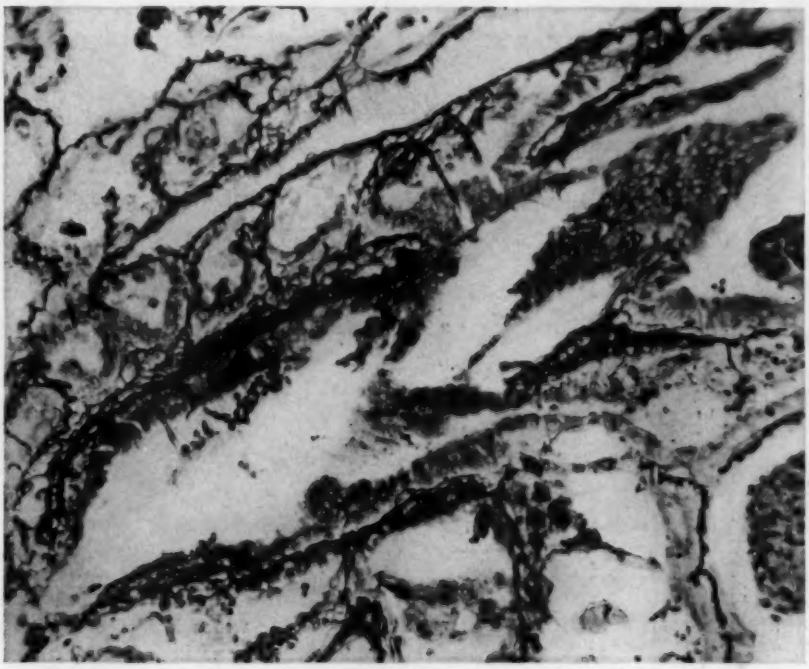

Fig. 6.—Section of cat's lung following intratracheal injection of liquid petrolatum. It was stained by Perdrau's silver nitrate method. The peribronchial alveoli are invaded by proliferated basal cells which line the alveolar septums, giving the impression that the air sacs are normally lined by cuboidal epithelium.

the same picture in experiments on cats and rabbits with the intratracheal injection of oils. In all instances, when the ciliated columnar cells were destroyed or damaged, the "basal" cells only showed active regeneration (mitoses and proliferation); they formed many layers of small cuboidal or "oat" shaped cells and also invaded the peribronchial alveoli (figs. 6 and 7).

Experimental and clinical investigation show that cancer is always preceded by a process of regeneration. The development of epithelioma

in areas subjected to roentgen rays, epithelioma of the lip of those who smoke pipes, and tar and paraffin cancers are widely known. Observation has shown that cancer of the lungs, too, usually follows a long-standing chronic inflammation. Ewing,[1] for instance, expressed the belief that the chief etiologic factor of carcinoma of the lungs is tuberculosis, and other observers found it in patients with bronchiectasis, and with pulmonary syphilis. Tuberculosis, syphilis and other long-standing pathogenic infections of the lungs, such as chronic inflammatory processes, cause damage of the bronchial mucosa followed by excessive (pathologic) regeneration which eventually leads to the development of an epithelial malignant disease.

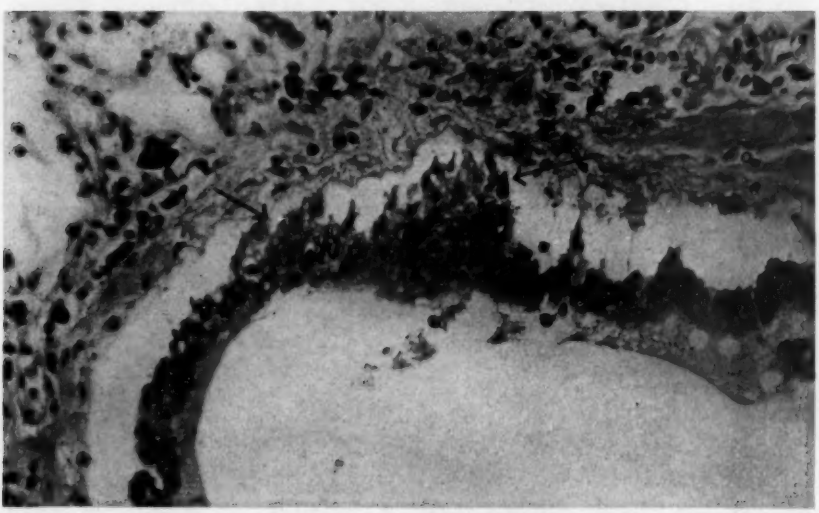

Fig. 7.—A section from a human bronchus, showing the early stage of basal cell proliferation. The peribronchial tissue shows signs of inflammation. The bronchial mucosa is detached from the basal membrane which is edematous, being invaded by small lymphocytes. The cellular agglomerations indicated by arrows are regarded as the beginning stage of protoplasia (metaplasia).

The apparent lack of any activity in the process of bronchial repair on the part of the ciliated columnar epithelium in the presence of an active "basal" cell proliferation seems to me to favor the conception that only the latter cells are concerned in the genesis of an epithelial malignant disease in the lungs.

METAPLASIA AND PULMONARY CANCER

Postmortem material reveals that a large percentage of all pulmonary tumors are of the basal or the squamous cell type. Since normally such cells are absent in the lungs, the origin of these tumors was said to be due to a conversion of the ciliated columnar cells into the squamous

epithelial variety. The condition was therefore designated as metaplasia (fig. 8). This conception of a direct transformation of one "well characterized tissue into another equally well characterized but morphologically and functionally different" was advanced for the first time by Virchow.[10] This hypothesis, however, is not borne out by close observation. In the first place, as already noted, it is improbable that the "apotent" ciliated columnar epithelium is able to transform itself into

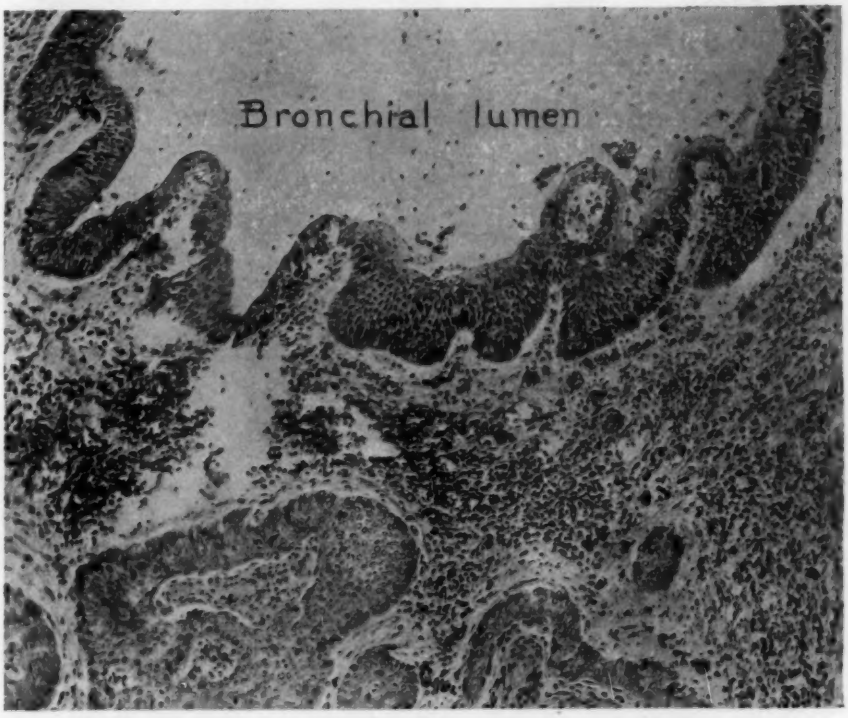

Fig. 8.—Metaplasia of bronchial epithelium in a human lung. The bronchial mucosa is made up of a layer of cells closely resembling that of the cutis. In another segment the mucosa of the same bronchus shows active proliferation of basal cells with mitoses. The membrana basalis is dissociated and largely obliterated. The tissue between the cartilaginous plates and the basal membrane is edematous, contains newly formed blood spaces, and is heavily infiltrated with lymphocytes and plasma cells. In three small bronchioles surrounded by the inflamed tissue, the lining shows a malignant condition. Hematoxylin and eosin; × 110.

any other variety of cell. Another point was raised by Wells,[11] who said:

10. Virchow, R.: Ueber Metaplasie, Virchows Arch. f. path. Anat. **97**:410, 1884.

11. Wells, H. G.: Primary Squamous-Cell Carcinoma of the Kidney as a Sequel of Renal Calculi, Arch. Surg. **5**:356 (Sept.) 1922.

The formation of metaplastic squamous epithelium brings forward two puzzling topics, one chemical, the other embryologic. The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin, which is a definite chemical compound, formed normally, as far as is known, by the cells of ectodermal origin, including the neurokeratin of the central nervous system. When cells of endodermal origin, such as those lining the renal pelvis or the uterus, take on the function of forming this peculiar, insoluble, sulphur-rich, indigestible, protective chemical, keratin, they have assumed a chemical function which seems to be far removed from their normal capacity. Hence we must conclude that metaplasia involves not only a morphologic but a chemical transformation of cells.

For tumor pathology, another problem arises. When cells assume the proliferative activity that is characteristic of malignant disease, they usually lose their more recently acquired functions and retake chiefly the simple vegetative function of proliferation. But when a transitional or columnar epithelial surface becomes squamous through metaplasia, and the same protracted irritation that produced the metaplasia continues until cancer results, we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing, squamous cell carcinoma. One would expect the epithelium to approach its original, simpler embryonal character, rather than exhibit and return so profound and recently acquired an alteration as the production of keratin.

At the present time, the original conception of Virchow [10] of a direct metablasia has received a new interpretation: Observers emphatically deny the authenticity of a direct transformation of the endodermal columnar cell into an ectodermal squamous epithelial cell. Borst,[12] for instance, stated that there is no such thing as direct metaplasia with the persistence of cells, and other workers affirmed that only those cells which are endowed with "dormant" developmental potentialities may undergo new changes. Those cells, however, which have become entirely "apotent" do not regenerate and still less become transformed into a new cellular type. Most pathologists regard the so-called metaplasia as a complicated biologic process of regeneration with new formation of cells (neoplastic phase) which is ultimately followed by a differentiation (metaplastic phase). Cells with embryonic or postembryonic potentialities are liable to such a metamorphosis, whereas the ciliated columnar epithelium lining the bronchi is a fully differentiated and therefore a "nonreversible" cell.

What then, is, the origin in the lung of the "foreign" squamous epithelial cells?

The idea of a few observers that this cell is apparently an embryonic rest could not be corroborated by most diligent investigators. Clinicopathologic and experimental studies convincingly point to another source. It would appear that the "basal" cells already referred to,

12. Borst, M.: Allgemeine Pathologie der malignen Geschwülste, Leipzig, S. Hirzel, 1924: Das pathologische Wachstum, in Aschoff: Pathologische Anatomie, Jena, G. Fischer, 1923, vol. 1, p. 582.

which lie close to the membrana basalis of the bronchus, are the progenitors of the stratified squamous epithelium.

Teutschländer [13] observed the process of "transformation" of this cell in the bronchi of rats that died of bronchopneumonia; Goldzieher [14] found it in the lungs of children who died of diphtheria and measles,

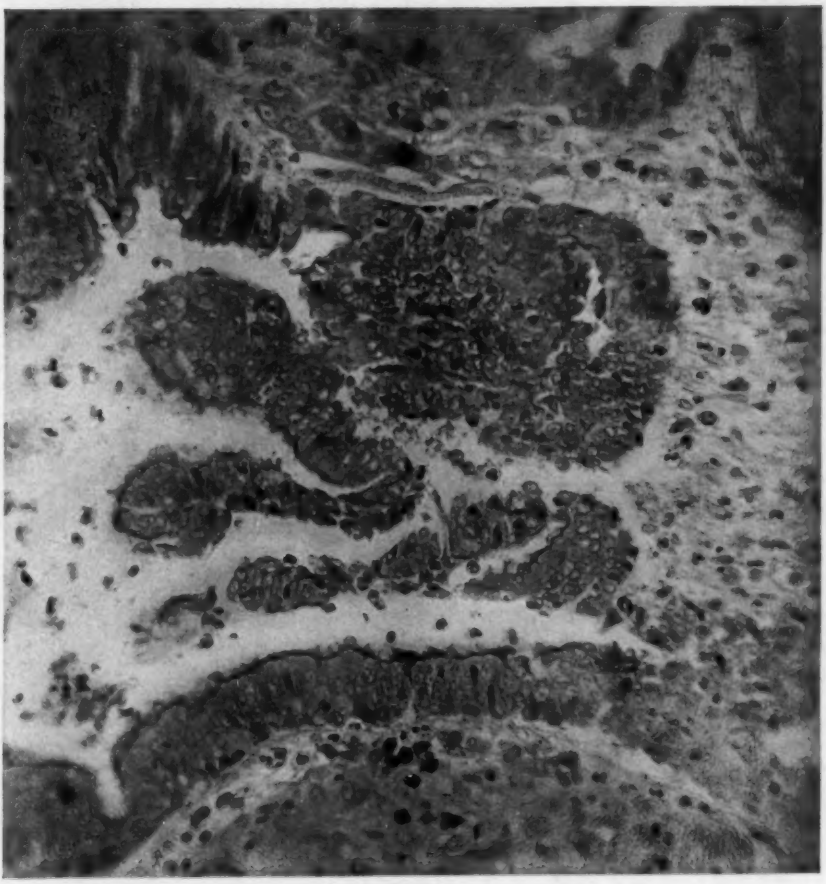

Fig. 9.—Protoplasia of bronchial epithelium of human lung. The ciliated columnal epithelium is pushed away by the protoplastic basal cells which are agglomerated in masses. The columnar epithelium shows no signs of regeneration, as evidenced by mitoses and proliferation.

13. Teutschländer: Ueber Epithelmetaplasie mit besondere Berücksichtung der Epidermisierung der Lungen, Centralbl. f. allg. Path. u. path. Anat. **30**:433, 1919.

14. Goldzieher, M.: Ueber Bazalzellwucherungen der Bronchialschleimhaut, Centralbl. f. allg. Path. u. path. Anat. **29**:506, 1918.

and Askanazy [15] outlined this pathologic phenomenon in the lungs of persons who died of pneumonia following influenza.

Of particular interest are the experimental studies by Wolbach [16] on changes in the tissues following deprivation of fat-soluble vitamin A. By feeding rats a deficient diet, he noticed that the "missing factor" caused a widespread keratinization of epithelium. In the respiratory tract the process began in numerous foci, and the rate of the cellular growth was rapid as attested by numerous mitoses of the basal cells. What is more, these experiments have shown that the basal cells begin to proliferate even before any changes are detectable in the columnar epithelium which only subsequently degenerates and separates from the basal membrane. It is also interesting that this process is not necessarily brought forward by a previous inflammation; a mere stimulus generated by a "missing factor" from the food caused an "alarm" among the cells, followed by their multiplication and differentiation.

Apparently this pathologic phenomenon occurs in numerous bronchopulmonary diseases. Askanazy [15] found metaplasia in a high percentage of patients who died of pneumonia following influenza, and Goldzieher [14] noticed the same thing in patients with measles and diphtheria. In a recent study, Smith [17] also observed metaplasia in children with whooping cough. Two examples of this condition, one an early stage of the condition and the other a fully developed metaplasia, have recently been observed. The first was in a girl, aged 17 years, who died of aleukemic lymphadenosis. The lungs contained numerous bacteria, and the alveoli were in areas filled with fibrin. The bronchi showed numerous polymorphonuclear leukocytes, desquamation of the columnar ciliated epithelium and a proliferation with transformation of the basal cells into transitional cells (figs. 7, 9 and 10).

In the second example of a thymoma with pulmonary metastases, the lungs showed a great deal of fibrosis and round cell infiltration. The condition found in many bronchi is demonstrated in figure 9. From this picture it will be seen that the "basal" cells only have proliferated, while the columnar cells are merely pushed away.

The peculiar character of the differentiation of these cells into squamous epithelium is interpreted in the light of the ontogenesis of the tissue in question. From an embryologic standpoint the tracheobronchial tree and the esophagus represent two sister organs, and their

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15. Askanazy, J.: Ueber die Veränderungen der grossen Luftwege besonders ihre Epithelmetaplasie bei der Influenza, Cor.-Bl. f. schweiz. Aerzte **49**:465 (Jan. 18) 1919.

16. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, J. Exper. Med. **42**:753, 1925; Vitamin A Deficiency in the Guinea-Pig, Arch. Path. **5**:239 (Feb.) 1928.

17. Smith, Lawrence W.: The Pathologic Anatomy of Pertussis, Arch. Path. **4**:732 (Nov.) 1927.

development goes parallel. Schridde [18] has produced evidence to show that in the earliest stages of development the esophagus is lined with one layer of cuboidal cells, which at the fifth week becomes doubled and at the tenth acquires goblet cells and ciliated columnar epithelial cells. Whereas in the bronchi the development ends at this phase, in the esophagus these cells degenerate and desquamate, being subsequently replaced by a transitional epithelium and finally by a stratified squamous epithelium. It is assumed, then, that in pathologic processes the

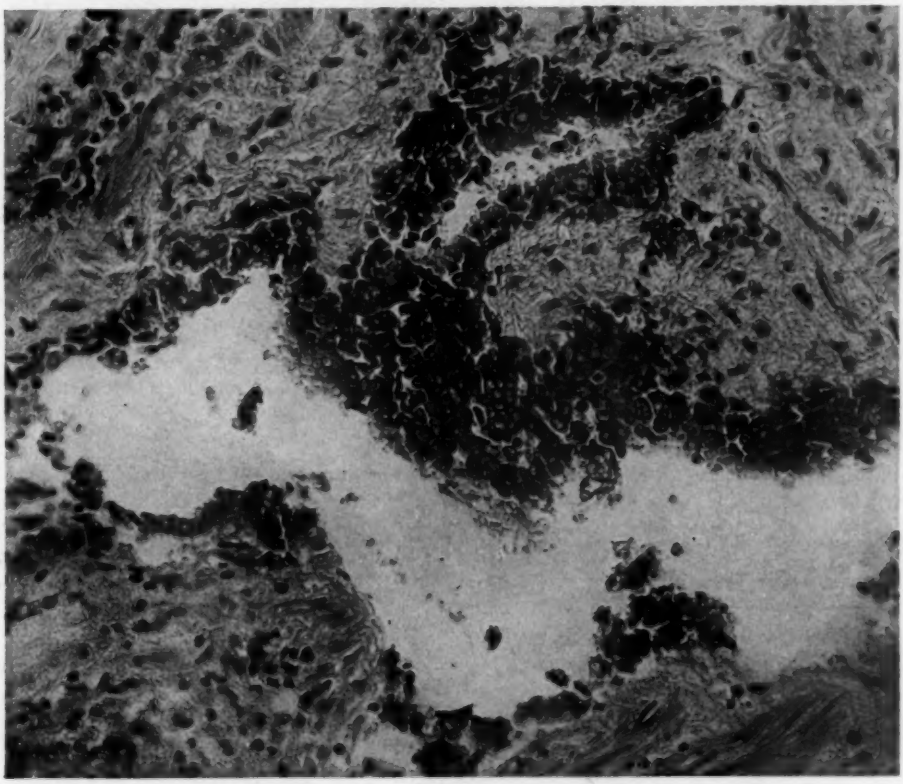

Fig. 10.—Protoplasia of bronchial epithelium. Section from a human bronchiolus respiratorius, first order, showing proliferation of the basal cells forming many layers of stratified squamous epithelium. The bronchiolar basal membrane being destroyed, these cells invade the surrounding granulation tissue where they are arranged in a tubular manner. Methylene blue and eosin; × 300.

bronchus, in its regenerative attempt, merely reaches in adult age the stage which the esophagus has attained as an embryo.

It will be seen, therefore, that the process is not a transformation of the adult columnar epithelium into a squamous type, but that a

18. Schridde, H.: Die Entwicklungsgeschichte des menschlichen Speiseröhren Epithels, Wiesbaden, 1907.

development of undifferentiated cells followed by proliferation and differentiation occurs. The phenomenon is consequently not that of metaplasia, but is one of protoplasia (indirect metaplasia).

Briefly, then, the process of repair or regeneration in the bronchi is performed by the bronchial "basal" cell only. In physiologic repair, these cells differentiate merely into the normal lining of the bronchus. But when the process is pathologic, their fate depends in all probability on the nature of the stimulus. Thus, they may differentiate into metaplastic islands and so remain indefinitely, or they may develop into a malignant condition. In fact, most pathologists regard the phenomenon of metaplasia as being a precancerous stage.

REPORT OF CASES

Two patients with primary carcinoma of the lungs came to my attention: In one the histology of the tumor was that of a basal cell cancer; in the other, it was a typical keratinizing epidermoid carcinoma.

CASE 1.—*History.*—A man, aged 38, a gardener, entered the hospital with the complaint of progressive weakness and loss of weight of eight months' duration. The past and family histories were unimportant.

One week before admission, swelling was noticed in front of the left shoulder. For three or four weeks, he had a cough coincident with a cold, and raised slight quantities of normal-looking sputum. He became so weak that he could hardly sit up in bed. He had been hoarse for a month. He had noticed clubbing of the fingers, of the left hand particularly, during the last two weeks.

Examination.—Evidences of loss of weight and cachexia were found. Edema involved the left shoulder and the apical regions. The expansion of the chest was less marked on the left. Respirations were 26, and of shallow depth. The thorax was narrow and ptotic; the heart and aorta showed no pathologic condition. The veins in the left arm and neck were dilated, and slight dilatation was present in the right arm.

In the lungs, the expansion was diminished on the left side. Vocal fremitus was diminished on the left side and was practically absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border and to the posterior axillary line. Anteriorly, it was dull at the apex, up to the second interspace; below that, it was normal for an interspace and then markedly tympanitic up to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed diminished bronchial breathing posteriorly at the apex down to the scapula. Below that, for a distance of two or three interspaces, the breath sounds were purely bronchial and close to the ear; at the base, there was distant bronchial breathing. The whispered voice corresponded to the breath sounds. Anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base there was distant bronchial breathing. The right side did not show any pathologic condition. The voice did not sound abnormal. Except for the clubbed fingers, which were more marked on the left, the physical examination revealed nothing remarkable.

During thoracentesis, a few small pieces of necrotic material were obtained which on examination showed the presence of carcinoma.

The patient died after a stay of twenty-two days in the hospital.

Necropsy.—The body was poorly nourished and cachectic, measuring 170 cm. in length. The external examination revealed clubbed fingers, more pronounced on the left hand; a large decubitus over the sacrum; a slightly prominent abdomen, and a hard, palpable lymph node in the right axilla. The peritoneal cavity contained 150 cc. of clear, straw-colored fluid. A membranous exudate about 2 mm. thick was found overlying the lower portion of the sigmoid colon.

Pleural Cavities: The right cavity was free and contained about 100 cc. of a clear yellowish fluid. Both the parietal and the visceral pleurae showed no

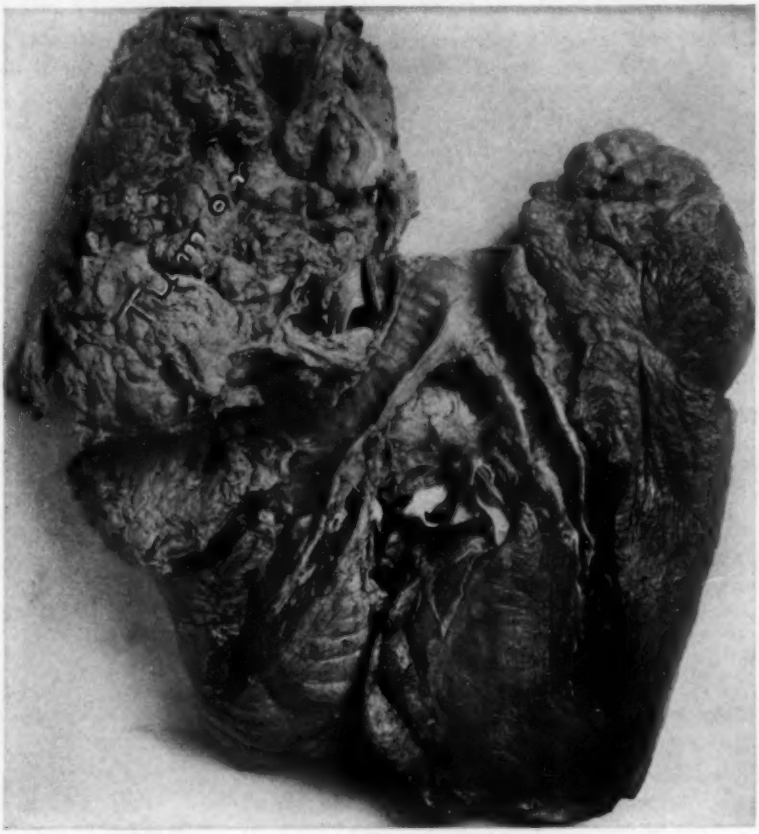

Fig. 11 (case 1).—Primary basal cell (nonkeratinizing) epithelioma of the left bronchus. The main stem of the left bronchus which enters the lower lobe and its ventral and dorsal branches show no disease. The first branch of the left bronchus is also normal, but its lower and middle intrapulmonary branches are patent only for about 3 cm. and are occluded at the end by tumor.

inflammatory changes or invasion by tumor. The left cavity contained about 300 cc. of fluid similar to that found on the right side. The cavity was free, except at the apex and posteriorly, particularly along the spine and posterior wall of the chest where it was obliterated by extremely strong adhesions. The left lung appeared normal in front and in the axillary region from the beginning of the third rib downward; posteriorly, only the lower lobe was free from tumor. The visceral pleura in the areas untouched by the new growth was normally thin and

translucent, and the lung was pale and slightly emphysematous. The lungs and heart were separated from the pleural cavity *en masse*.

Owing to strong adhesions, the apical part of the tumor and that part along the spine were torn on removal, a portion being left in the chest. When the visceral pleura was thus torn, it seemed that the tumor walled off by the pleura shelled out from the latter and appeared twice as large as when seen in situ. The tumor was grayish white, moderately firm and somewhat friable. It was composed of one large mass, and on the surface in front, two nodules, from 3 to 5 cm. in diameter, were seen. The tumor was sharply demarcated from the pulmonary parenchyma.

Trachea and Bronchi: The trachea appeared normal. Its mucosa was pale and covered with a colorless, frothy fluid. The right bronchus and its divisions showed no changes. The main stem of the left bronchus entered the lower lobe of the lung as usual, and its dissected ventral and dorsal branches were patent and showed no pathologic condition. The first branch of the left bronchus (normally distributed to the superior lobe) was normal throughout. Two of its larger intrapulmonary branches, the lower and middle, were patent and appeared normal only for about 3 cm. and were occluded at the end by tumor. The other intropulmonary branches distributed in the superior part of the upper lobe could not be traced at all, being entirely surrounded by tumor and destroyed.

Lymph Nodes: The tracheal, tracheobronchial and mediastinal lymph nodes did not show any invasion by tumor. The nodes below the bifurcation seemed to be enlarged, without, however, any invasion by the tumor. The third and fourth ribs at the junction of the vertebrae and two thoracic vertebrae were eroded in the areas of the tumor attachment, but no invasion of the bone could be demonstrated. The other organs did not reveal the presence of any new growth or other noteworthy changes.

Microscopic Examination.—Lungs: Sections taken from different parts showed the tumor to be composed of polyhedral cells having a large cytoplasm and a voluminous vesicular nucleus. These were arranged in columns and strands from 2 to 3 cells broad, which showed anastomosis and branching. In one section, the cells had a somewhat tubular arrangement; their nuclei were compressed, pushed toward the periphery and had a rosetlike appearance. In another section, the tumor was rather solid, being arranged in small clumps of cells or short rows of single cells. The cells contained a great variety of inclusions, resembling in areas the "parasites" described by some writers and, occasionally, the so-called "bird's eye" inclusions. Round globules of a different size, stained black with methylene blue eosin, were conspicuous all over the sections. There was no keratinization or pearl formation. A great deal of fat was seen in the cells, as well as between the cells.

The stroma of the tumor consisted of a loose, edematous connective tissue infiltrated with small round cells, and here and there with single tumor cells. The tumor was sharply demarcated from the pulmonary parenchyma, which showed compression of the alveoli and thickening of the alveolar wall. Mitotic figures were rarely seen. The lymph nodes showed no signs of tumor. The other organs, except for the kidneys, which showed an early parenchymatous nephritis, were not remarkable (figs. 12 and 13).

The pathologic diagnosis was basal cell carcinoma of the left lung originating in a small division of the left bronchus; chronic, adhesive, fibrous pleuritis; hydrothorax (bilateral); peritonitis; decubitus, clubbed finger and cachexia.

Comment.—The histologic and clinical features of the tumor in this case were that of a typical (nonkeratinizing) basal cell cancer. Like most basal cell cancers of the skin, the present tumor did not metastasize,

being, therefore, relatively benign. It is interesting whether a pulmonary cancer of this variety would be as sensitive to radium or to roentgen rays as is the cutaneous new growth with a similar structure. The bronchiogenic origin of these tumors is at present accepted by most pathologists. Its peculiar microscopic appearance, however, as referred to, is attributed to a transformation of the columnar ciliated epithelium, which is apparently an error. Indeed, the lungs in this case were examined at a period when the tumor was in an advanced stage, which made histogenic studies futile. Nevertheless, the microscopic architecture and

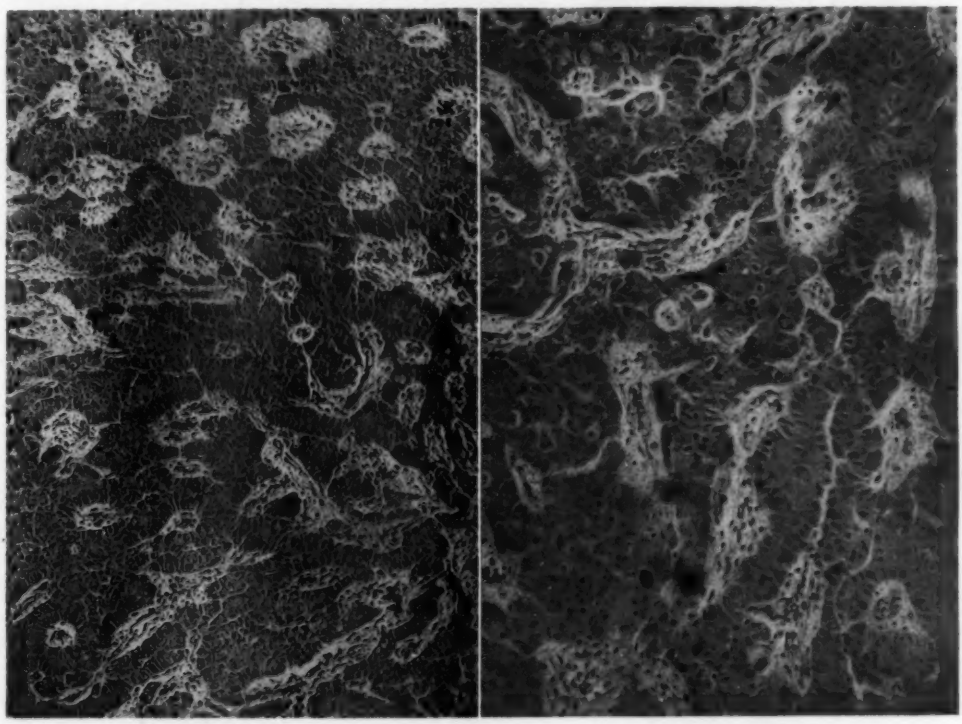

Figure 12 Figure 13

Figs. 12 and 13 (case 1).—Primary basal cell (nonkeratinizing) epithelioma of the left bronchus. The tumor is composed of polyhedral cells arranged in columns and strands which anastomose and branch. They also form "tubules." The gross appearance of the tumor is given in figure 12.

the clinical characteristics of the growth, when added to the biologic potentialities of the bronchial basal cell, seem to favor the opinion that the cancer did not originate through metaplasia from the ciliated columnar epithelium, but developed as a result of protoplasia of the undifferentiated basal cells of the bronchial mucosa.

In the following case the differentiation of these cells went one step further, leading to a typical keratinizing squamous cell carcinoma.

CASE 2.—*History.*—A man, aged 64, entered the medical service of the hospital, complaining of cough and fever. Fourteen months before, he had some wheezing and shortness of breath, which lasted for about six months. He entirely recovered from this and was well until six months before admission, when he began to have an unproductive but distressing cough which varied with the weather; the cough grew worse during a cool spell and was increased by exertion. This condition had continued; there was little sputum, but on one occasion the patient had hemoptysis. The only pain he had had was substernal and in the epigastrium after paroxysmal coughing. He had lost 10 pounds (4.5 Kg.) in the last year. The roentgen examination two months previous to admission to the hospital showed a rounded shadow just to the right of the heart shadow, suggestive of a mediastinal tumor.

Examination.—Dulness was present over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area. The heart was apparently displaced to the right. The temperature ranged between 99.8 and 103.8 F.

The roentgen examination on entrance showed marked clouding of the right base. The heart, trachea and mediastinum were displaced to this side. The "rounded shadow" originally noted was not evident, apparently being obscured by the heart shadow.

The patient remained in the hospital twenty-two days during which time he lost about 10 pounds (4.5 Kg.). Except for signs of a slight amount of fluid in the right side of the chest, the clinical picture did not change. He was discharged, three weeks after admission, unimproved.

Two weeks later, he was readmitted to the hospital. On physical examination, no marked changes were noted. The patient remained in the hospital three days, and was discharged with the diagnosis of carcinoma of the lungs. At home, he developed occasional hemoptysis. The cough and fever continued. He died about two years after the onset of the first symptoms.

Necropsy.—The necropsy was performed by Dr. S. B. Wolbach, fifteen hours post mortem. The body was poorly nourished and did not show any marks worthy of note. The peritoneal cavity, except for the presence of about 750 cc. of clear yellow fluid, was not remarkable. The pericardial cavity was distended with about 150 cc. of a dark red fluid, containing flecks of fibrin. The pericardial surfaces were covered with a red, shaggy, adherent, fibrinous material. The heart was normal in size. The striking feature of the organ, in addition to the fibrinous exudate, was the presence of about fifteen elevated nodules from 4 to 12 mm. in diameter, which were distributed fairly uniformly over the right and left ventricles. On incision they were white, fairly firm and regular, and pressure caused droplets of white material to exude, which subsequent microscopic examination showed to be keratinized and necrotic epithelial cells.

Chest: The ribs and sternum were adherent on the right side to a thickened pleura along the anterior border of the right lung, and to a hard, firm mass overlying the ascending aorta. The tissues at the anterior mediastinum were edematous. The right pleural cavity was entirely obliterated by dense tissue. The left cavity was free and contained about 1 liter of clear, deep yellow liquid.

Lungs: The right lung was freed by stripping the parietal pleura, and the lungs and heart were removed *en masse* with the right side of the diaphragm. The pleura over the posterior border of the right lung ranged from 3 to 6 mm. in thickness, and consisted of dense, white, fibrous tissue with firmer white plaques, from 2 to 4 mm. thick, composed of friable tumor material. There were a few pigmented lymph nodes at the anterior border of the diaphragm which contained numerous white nodules.

When the trachea and bronchi were opened, the trachea, except for deep injection, was normal. The left primary bronchus also was normal. The right was practically occluded 2 cm. below the bifurcation (fig. 14). Anteriorly, the wall of the right primary bronchus was replaced by a friable, white tumor tissue which on pressure exuded soft, white material; on subsequent examination this proved to contain desquamated epithelial cells, the largest part of which were keratinized. The only branch of the right primary bronchus that could be found was one leading to the upper part of the right lobe, and the orifice of this bronchus

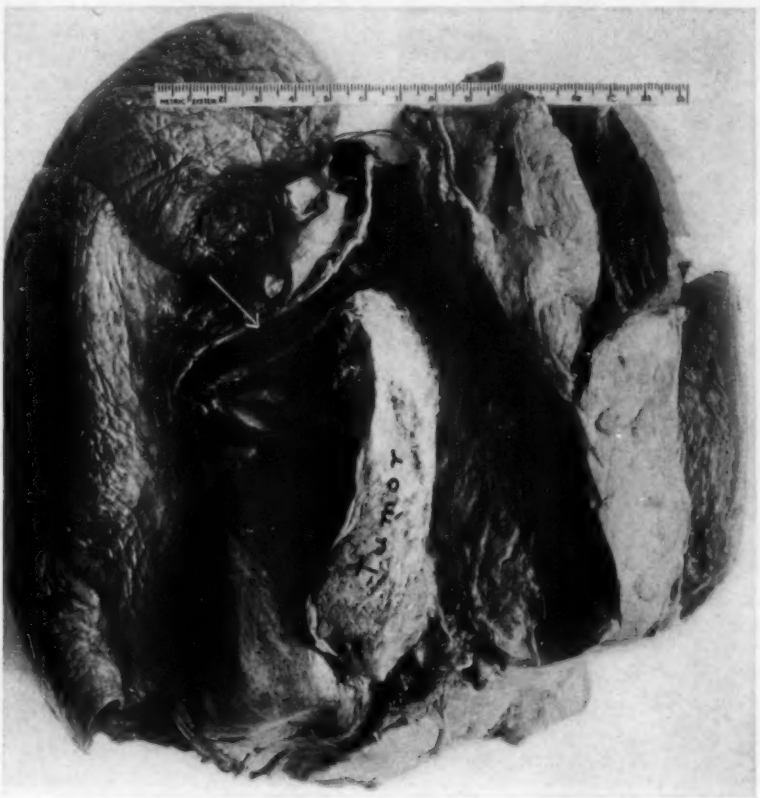

Fig. 14 (case 2).—Primary squamous cell epithelioma (keratinizing) of the right bronchus, showing the dorsal aspect of both lungs, trachea and main bronchi. The tumor is present in the right bronchus and the right lung. The left bronchus is indicated by the arrow.

was nearly completely occluded by tumor tissue. Below, the bronchus ended abruptly in a mass of friable tumor, from 1 to 3 cm. thick, which extended downward along the inner posterior margin of the lung for a distance of 8 cm. Anteriorly, the tumor, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer 1 cm. thick, which extended upward over the ascending portion of the arch. Two parallel incisions were made through the posterior borders of the lungs and showed that the whole lung was atelectatic, with here and there small bronchiectatic cavities. The whole of the upper lobe was tough and fibrous, and in the

peripheral portion of the lung were a few nodules, a few abundant in the lower lobe. The left lung was not incised but seemed to be normal. On the inner surface of the lower lobe, that is, in contact with the pericardium, there were two plaques of tumor, each a few millimeters thick and 1 cm. wide. The head was not opened. The other organs were normal.

Microscopic Examination.—Lungs: The tumor grew without any definite arrangement. Nests or masses of cells were scattered over the sections surrounded

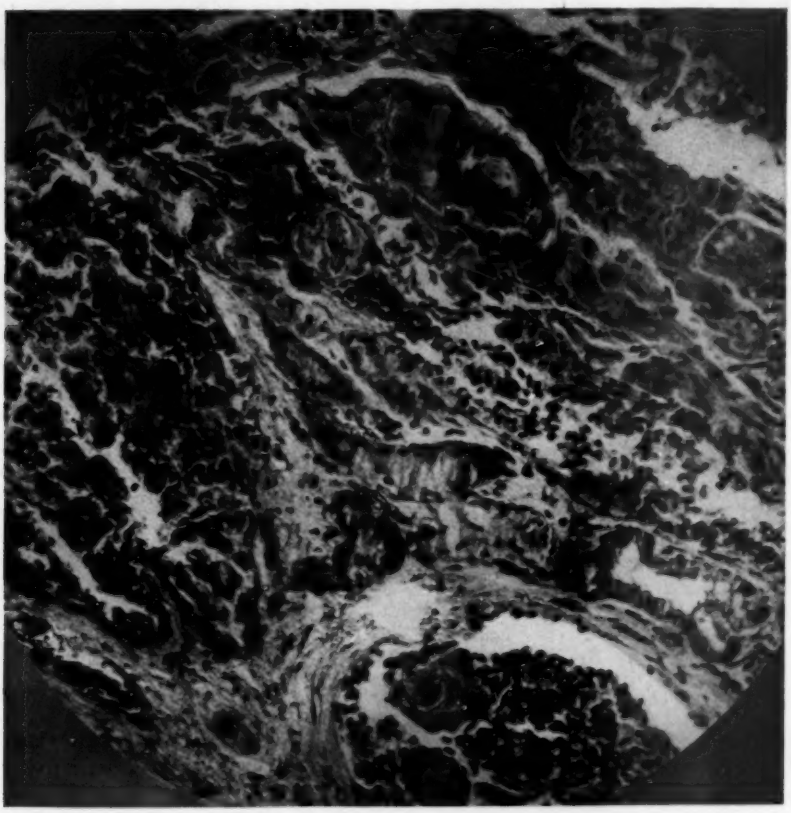

Fig. 15 (case 2).—Primary squamous cell (keratinizing) epithelioma of the right bronchus. The tumor cells are arranged in nests without any definite architecture. They show areas of keratinization and "pearl" formation. The gross appearance of the tumor is shown in figure 14.

by thick bands of dense fibrous tissue. The tumor cells individually were large, polygonal or elongated and irregular in outline. The cytoplasm was finely granular and stained blue. The vesicular nucleus occupied the greater part of the cell; it was large, rich in chromatin and contained a centrally located, deep stained nucleolus. The cells varied slightly in size. Large cells with many nuclei, resembling giant cells, were encountered here and there. In many areas, mostly in the center of the tumor mass, the cells had a tendency to arrange themselves in concentric layers. Here, the cells were usually larger than the tumor cells; their cytoplasm was stained deep red with eosin, and the nucleus seemed generally to

be smaller. These masses of cells had the typical appearance of the cornified epithelium encountered in the so-called "pearls" of the epidermoid carcinoma. Here, also, there was a definite tendency to "pearl" formation (fig. 15). These keratinized masses were seen in practically all sections. The pulmonary tissue adjacent to the tumor, but free from the new growth, showed extensive fibrosis in dense and avascular areas and in areas rather loose and richly supplied with blood. Macrophages loaded with a brown pigment were disseminated occasionally among the tumor cells and, more conspicuously, in the preserved and compressed or distorted alveoli. Anthracosis and round cell infiltration were seen here and there. The pleura showed invasion by a tumor which displayed the characteristics of the main tumor. The lymphatics were greatly distended by tumor nodules, which occupied the greater part of their lumen.

Esophagus: The tumor here was confined to the muscularis mucosa and submucosa and was identical with the pulmonary tumor. It was sharply demarcated from the normal tissue. The esophageal mucosa was intact. Mitotic figures in the main tumor, as well as in the metastases, were rarely found.

The pathologic diagnosis was epidermoid carcinoma originating in the right primary bronchus with metastases to the pleura, left lung, heart, regional lymph nodes and esophagus; hydrothorax (left); hemopericardium; ascites; amyloid degeneration of the spleen, and passive congestion of the liver.

Comment.—Here, then, is a cancer with histologic traits of a keratinizing epidermoid type which has led to widespread metastases. The problem of basal cell epithelioma and squamous cell epithelioma of the skin has been the source of numerous investigations. For particulars on the subject, a recent study by Montgomery [19] may be consulted.

Apparently in the lungs, too, this variety of cancer has its origin in the "basal" cell of the bronchial mucosa.

CONCLUSIONS

1. Carcinoma originating primarily in the lungs is bronchiogenic.

2. There is evidence that when the disease is found in the lungs it results from a pathologic (excessive) regeneration following chronic inflammation of the bronchial tree.

3. Of the three varieties of cells lining the bronchial mucosa, i.e., the ciliated columnar epithelium, the goblet cells and the "basal" cells, only the last are concerned in the process of regeneration of the bronchial mucous membrane. It is assumed, therefore, that these cells likewise serve as a sole matrix for primary bronchiogenic tumors.

4. Similarly, primary squamous cell epitheliomas and basal cell epitheliomas of the lungs do not result from metaplasia of the preexisting ciliated columnar epithelium, but originate through protoplasia (indirect metaplasia) of the undifferentiated basal cell of the bronchial mucous membrane.

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19. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

MULTIPLE HEMANGIOFIBROMA OF THE PULMONARY VALVE*

MILTON G. BOHROD, M.D.

CHICAGO

In 1898, when Guth [1] reported the third case of a tumor on a cardiac valve, he wrote: "In spite of their relative rarity there is a copious literature concerning primary tumors of the heart." From that time until this report of the twenty-fourth case the literature has grown immensely. About these small, harmless bodies and the related mural endocardial tumors much controversy has arisen, which has not yet subsided, for in Henke and Lubarsch's new "Handbuch der spezielle pathologische Anatomie," Ribbert devoted several pages to the discussion as to whether they are tumors. The discussion is all in the German literature, for, with the exception of the first few cases which were reported from France, the single report of Dean and Falconer [2] in England and the short report of Blumgart [3] in the United States, all the cases seem to have been found in Germany, Austria and Switzerland.

It is peculiar that however much these tumors may differ among themselves, they are sufficiently alike to be grouped by every one who writes about them into a single group, and that between them and the various conditions which they are supposed to resemble, there are no intermediate stages. Variously referred to as myxomas, pseudomyxomas or different kinds of fibromas, they may be divided into two groups according to location: those on the mural endocardium and those on the valves. Here the differences end, for histologically the two types resemble each other closely. The mural tumors, of which about seventy-five cases have been reported, may reach such large size as to fill an entire cardiac chamber, usually the auricle. In most cases they take their origin from the margin of the fossa ovalis. They are papillomatous, completely covered by endothelium, and are composed of loose tissue resembling myxomatous tissue. They may or may not contain many blood vessels or elastic fibers. They have been described

* Submitted for publication, March 8, 1929.

* From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Guth, H.: Ueber einem Fall von papillärem Myxom auf der Valvula tricuspidalis cordis, Pragr. med. Wchnschr. **23**:85, 1898.

2. Dean, G., and Falconer, A. W.: Primary Tumors of Cardiac Valves, J. Path. & Bact. **18**:64, 1913-1914.

3. Blumgart, L.: A Tumor of the Mitral Valve, Am. J. M. Sc. **134**:576, 1907.

as myxomas (Ribbert[4]), fibromas (Jaffé[5]), fibro-angiomyxomas (Fabris,[6] Csemez[7]) and hemangio-elastomyxomas (Brenner[8]) by authors who think of them as neoplasms, and as organized thrombi by those who do not believe in their neoplastic origin (Stahr,[9] Gödel,[10] Thorel,[11] Schwartz[12]). Similar structures have been reported in animals (Stahr,[9] Ackerknecht[13]).

In twenty-three cases of valvular tumor nodules reported, five were tumors of the mitral, six of the aortic, eight of the tricuspid and four of the pulmonary valve. All of them were observed accidentally at necropsy on patients who died from other causes. The ages varied from 19 to 86 years; the cases were about evenly distributed between the two sexes. Fourteen showed no signs of cardiac disease other than the tumors, three showed slight atheromatous thickenings of the valves, one an aneurysm of a mitral cusp, and only four showed evidences of chronic endocarditis. In view of the frequency of chronic endocarditis in any large necropsy material, the last mentioned observation is not significant. In only one case was there clinical evidence of endocarditis (Leonhardt[14]). Most of the tumors were pedunculated, but some were adherent to the valve by a broad base. A great many of them were papillary. All of them were single growths except those in the case of Boye (quoted by Husten[15]) who, in an inaugural dissertation which I have been unable to obtain, reported a case of two tumors of the tricuspid valve.

Twelve of the seventeen authors who reported cases of valvular tumors considered them as true tumors. Ribbert,[4] especially, empha-

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4. Ribbert, H.: Geschwülstlehre, ed. 2, Bonn, Cohen, 1914, p. 314.

5. Jaffé, R. H.: Das Myxom des Herzens, Beitr. z. path. Anat. u. z. allg. Path. **64**:533, 1918.

6. Fabris, A.: Fibro-angio-myxomatöse Neubildung des menschlichen Herzens, Virchows Arch. f. path. Anat. **241**:59, 1923.

7. Csemez, H.: Zentralbl. f. Herz. u. Gefasskr. **17**:304, 1925.

8. Brenner, F.: Das Haemangioelastomyxoma cordis und seine Stellung unter den Myxomen des Herzens, Frankfurt. Ztschr. f. Path. **1**:492, 1907.

9. Stahr, H.: Ueber die sogenannte Endokardtumoren und ihre Entstehung, Virchows Arch. f. path. Anat. **199**:162, 1910.

10. Gödel, A.: Zur Kenntnis der primären Herzgeschwulste, Zentralbl. f. Herz. u. Gefasskr. **14**:99, 1922.

11. Thorel: Pathologie des Herzens-Lubarusch und Ostertag, Ergebn. d. Allg. Path. u. path. Anat. **14**:11, 1910; Pathologie des Herzens, ibid. **17**:11, 1915.

12. Schwartz, D.: Ueber die sogenannten Myxome des Herzens, Virchows Arch. f. path. Anat. **264**:747, 1927.

13. Ackerknecht, in Joest: Spezielle pathologische Anatomie der Haustiere, Berlin, Richard Schoetz, 1919, vol. 4, pp. 317 and 466.

14. Leonhardt, A.: Ueber Myxome des Herzens insbesondere der Herzklappen, Virchows Arch. f. path. Anat. **181**:347, 1905.

15. Husten, K.: Ueber Tumoren und Pseudotumoren des Endokards, Beitr. z. path. Anat. u. z. allg. Path. **71**:132, 1923.

sized the true neoplastic nature of these bodies and thought most of them to be myxomas or angiomyxomas. He traced their origin to rests of myxomatous tissue which are sometimes found in otherwise normal valves. Authors, however, who have written about these reports have not been so unanimous. Those who consider the mural endocardial tumors as organized thrombi offer the same explanation for the valvular bodies. Thorel,[11] in two reviews on cardiac disease, insisted that all the cardiac masses, mural and valvular, are organized thrombi. Kirch,[16] who wrote the latest review on cardiac disease, steered between these two views and said that some of them may be neoplasms and others organized thrombi. Other authors (Leonhardt,[14] Curtis[17]) consider the tumors as the remains of old endocarditic lesions. The occasional discovery of concomitant chronic valvular endocarditis and the presence of lymphocytes and plasma cells within the tumors have been offered in support of their view. Zurhelle[18] reported a tumor-like body on the tricuspid valve the center of which was a large endothelial-lined blood space communicating with the right ventricle, the outside of which was connective tissue. He considered this growth as a persistent valvular blood cyst, such as is often found on the pulmonary valves of the new-born infant, which had become partly organized. He suggested that the organization of such persistent cysts might account for the polypoid valvular tumors. Koechlin,[19] who reported three cases of polypoid tumor, described in the same article thirty-five cases of Lambl's excrescences, fine, threadlike filaments projecting from the noduli arantii of the aortic valve. He expressed the belief that the valvular tumors in his case, and possibly in all other cases, were modified excrescences of this type. Leonhardt[14] had mentioned the same possibility several years before.

In the following case multiple tumor nodules were found on the pulmonary valve of a young man dying from abscesses of the brain. A primary focus for the latter was not discovered, so that in this instance the determination of the neoplastic or infectious nature of these tumors is perhaps of more than academic interest.

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16. Kirch, E.: Pathologie des Herzens, Lubarsch-Ostertag, Ergebn. d. allg. Path. u. path. Anat. **22**:1, 1927.

17. Curtis: Note sur un tumeur de la valvule mitrale, Arch. de physiol. norm. et path., 1871-1872, vol. 4.

18. Zurhelle, E.: Ueber ein aussergewöhnlich grosses persistierendes Blutknötchen an der Tricuspidalklappe eines Erwachsenen mit Bemerkungen über die Genese der sogenannten polypösen Herzklappenmyxome, Frankfurt. Ztschr. f. Path. **20**:319, 1917.

19. Koechlin, E.: Ueber primäre Tumoren und papillomatöse Exkreszenen der Herz klappen, Frankfurt. Ztschr. f. Path. **2**:295, 1908.

REPORT OF CASE

C. A., a white man, aged 20, entered the Research and Educational Hospital in coma. The history was obtained from his parents who were unusually cooperative but who knew little about his illness, which was recent, except that he had been complaining of severe headache and dizziness. So far as they knew, he had never had complaints referable to the heart. Signs of increased intracranial pressure and persistent high temperature and leukocytosis led to the diagnosis of probable

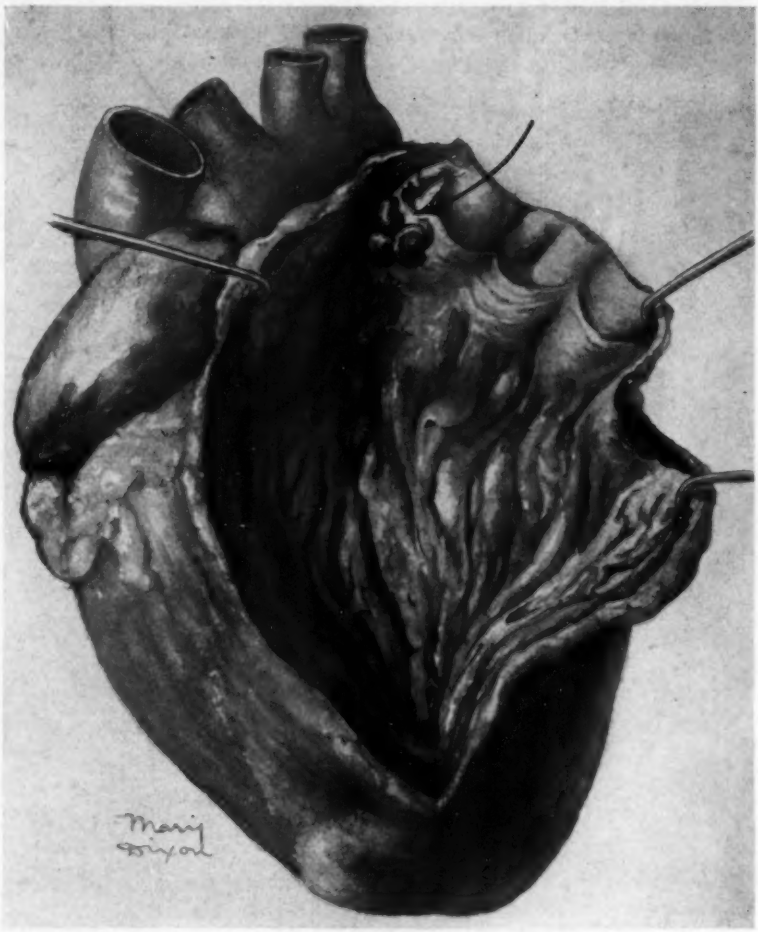

Fig. 1.—Hemangiofibroma of the pulmonary valve.

abscess or tumor of the brain, and the neurologic department localized the lesion in the frontal lobe. The patient died after two days in the hospital.

Necropsy performed within four hours after death showed, besides the peculiar condition of the heart, two abscesses in the right frontal lobe of the brain, right internal hydrocephalus, acute splenic tumor, cloudy swelling of the liver and kidneys and a slightly enlarged thymus gland. The tonsils appeared to be normal,

even under microscopic examination. The middle and internal ears and the accessory nasal sinuses were free from pathologic changes. The primary focus for the abscesses in the brain was not found.

The pericardial sac was normal and contained no fluid. The heart weighed 265 Gm. and was about the size of the patient's fist. The myocardium was pale reddish-brown and firm. In the left ventricle, it was 12 mm. thick; in the right, 3 mm. The mitral, aortic and tricuspid valves were smooth and thin and showed no abnormal condition.

The right anterior and the posterior cusps of the pulmonary valve were of normal appearance. On the left anterior cusp (fig. 1) there were three spherical

Fig. 2.—Section through two tumor nodules, the adjacent valve insertion and the pulmonary artery. Weigert's stain for elastic tissue; × 10.

bodies, 4 by 4 by 2 mm., 7 by 6 by 4 mm. and 6 by 4 by 3 mm., and one ovoid body 10 by 5 by 4 mm.; all were attached to the ventricular aspect of the leaflet by broad bases without the intervention of pedicles. The ovoid body was attached at the junction of the valve leaflet and the ventricular endocardium and at the extreme left; the round bodies were also closer to the insertion of the cusp, leaving above them a free portion, from 3 to 4 mm. long, of normal valve tissue. The noduli arantii was normal. The surfaces of these nodules were smooth and reddish brown, with lighter orange-brown spots the size of a pin point. They

were of rubbery, elastic consistency. There were no thrombi attached to them, nor was there evidence of thrombosis elsewhere in the heart. The whole heart was fixed in Kaiserling's solution. Then a block was removed which included portions of two tumor nodules and their attachments, the cusp, the pulmonary artery and a small portion of the ventricular myocardium (fig. 2). Sections from this were stained with hemalum-eosin, van Gieson's stain and Weigert's stain for elastic fibers.

Microscopic examination of the myocardium revealed no pathologic condition with the exception of occasional fine droplets of fat near the nuclei of a few of the fibers. Sections through the tumor nodules and the valve showed the following:

Fig. 3.—Section through the attachment of the tumor. The darker strands stained red; the lighter thick walls around the vessels stained yellow. Van Gieson stain; photographed through a green filter; × 140.

In the elastica stain a continuous heavy band of elastic tissue passed immediately beneath the subendothelial connective tissue of the valve, downward through the junction of the tumor and the valve to the ventricle and appeared just beneath the endothelial lining of the mural endocardium. Beneath this layer the valve appeared to be normal and contained no blood vessels or cellular infiltrates. Outside of this layer there was a triangular area the base of which was composed of the elastic layer described; the apex, of the fissure between the two

nodules, and the sides, of the nodules themselves. Within this area (fig. 3) there were wide, endothelial-lined blood spaces, the thick walls of which were made up of loose concentric layers of cells which stained yellow by the van Gieson method and which had long, spindle-shaped and round nuclei. In these walls there were many concentric rings of elastic tissue, one outer ring around each vessel being more prominent than the rest. The tissue between these vessels was made up of relatively acellular connective tissue which stained red by the van Gieson method.

The tip of this triangle, at the junction of the two nodules, was rich in short, thin elastic fibers. The tumor nodules were completely enveloped by a single

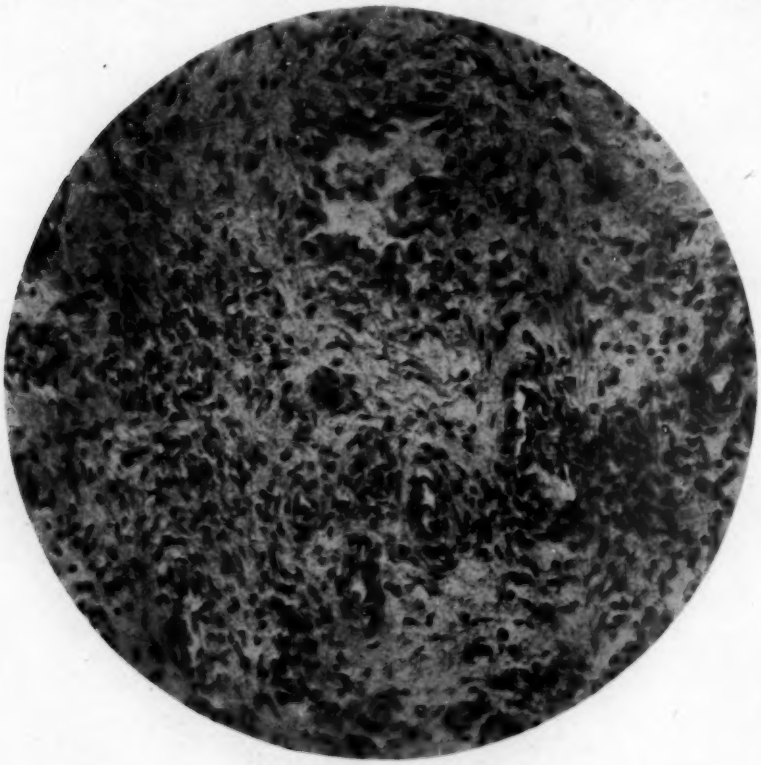

Fig. 4.—Section through the interior of the tumor. Note the mantles of cells around all the small vessels. Hemalum and eosin; × 300.

layer of flat endothelial cells. Immediately beneath this, there was a thin layer staining pink by the van Gieson method and containing long, spindle-shaped nuclei arranged parallel to the surface. The interiors of the nodules were similar and were composed of blood vessels and interstitial connective tissue (fig. 4). The blood vessels were numerous and diffusely scattered in all parts of the tumors except in the subendothelial connective tissue, in which they were entirely absent. In some places they were separated from each other by only a few cells, and made up almost all the tissue. They varied much in size, but, except for the capillaries, which were few, they all showed essentially the same structure. The

linings were prominent; the endothelium-like cells were numerous and bulged into the lumen of the vessel. Around these there appeared concentric rings of cells that stained yellow by the van Gieson stain and contained large, plump, spindle-shaped nuclei arranged concentrically around the lumen. Even the smallest vessels of capillary size contained at least two such rings of cells and the larger ones from five to eight, so that in most cases the thickness of the vessel wall exceeded that of the lumen. There was no division into layers in even the largest vessels; at most, the innermost layer was slightly more prominent than the rest. In the largest vessels, a few elastic fibers could be made out, but most of them contained no such fibers. The interstitial tissue was made up largely of long, spindle-shaped cells with thin, cigar-shaped nuclei. It was everywhere cellular; in some places it was loose, and the cells assumed a stellate appearance with long, branching processes, which gave it the appearance of myxomatous tissue. This myxomatoid tissue was especially marked near the free margin of the tumors. Clumps of golden yellowish-brown pigment were found in several places, especially near the base of the tumors. Lymphocytes in small numbers were found scattered through the attached portions of the tumors, and a few plasma cells were seen. One small accumulation of lymphocytes was found at the base of one of the tumors.

COMMENT

In this case there seemed to be a neoplastic process. The most striking structures were the vessels. Identical pictures were seen by Brenner [8] in what he called a hemangio-elastomyxoma attached to the fossa ovalis; he aptly described these vessels as consisting of a mantle of several layers of round and elongated cells, not divided into layers. Such vessels are seen in the embryo and remind one again of Ribbert's contention that these valvular tumors originate from embryonic rests within the valves. The other changes may be considered as retrogressive. Hemorrhages within benign tumors are not uncommon, and in a tumor situated on a valve which moves up and down at the rate of from sixty to eighty times a minute they are rather to be expected. The accumulation of lymphocytes and plasma cells about such liberated blood pigment is also not unusual.

It is noteworthy that in spite of the large size of the nodules and in the complete absence of portions of thrombi or definitely inflammatory tissue from which they may have arisen there should be no avidence of shrinking such as invariably occurs in the process of organization. This was emphasized by Ribbert,[20] who maintained that the endocardium is incapable even of organizing such large thrombotic masses. In the cases of mural tumors this is even more striking, for in a tumor filling an entire dilated auricle no contraction of scar tissue is seen. The tumors in this case, as in most others, are cellular and appear to be growing. Their apparent encapsulation by typical

20. Ribbert, H., in Henke and Lubarsch: Handbuch der spezielle pathologische Anatomie, Berlin, Julius Springer, 1924, vol. 2, p. 276.

connective tissue which seems to be separate from the tumor proper is also suggestive of a neoplastic process.

In a general survey of all the cases reported it seems to me to be necessary to consider the etiology of the valvular and mural endocardial tumors together because of their similarity. In both types the great infrequency of other cardiac changes, during life and post mortem, is striking, especially in view of the frequency of both intracardiac thromboses and endocarditis as primary causes of death and as incidental necropsy observations. A rare consequence of a common chronic condition, without any signs of that condition in the greatest number of cases, is not likely to occur. The entire absence of stages intermediate between thrombi or infective vegetations and these tumors is also noteworthy. In every case either the condition is definitely a thrombus or it is a peculiar "pseudomyxoma" which the observer thinks may have been a thrombus; never does he seem to be uncertain into which class to put them. When the tumors are papillary, this character is considered, especially by Jaffé [5] and Ribbert, to be that of a blastomatous growth.

The suggestion of Zurhelle [18] that these tumors are organized blood cysts may apply in a few cases, but the same arguments against other thrombotic processes apply here as well. Koechlin's hypothesis that the valvular tumors are modified Lambl's excrescences is, I think, untenable in view of his own report of thirty-five cases of typical excrescences, all similarly situated and similarly constructed, contrasted with his three tumors which, while all different, resembled each other much more than they did the Lambl bodies.

Finally, in spite of the rarity of all tumors of the heart, secondary as well as primary, primary sarcomas originating in the endocardium do occur (Husten,[15] Karrenstein [21]), and wherever there are malignant mesenchymal tumors, benign tumors may also occur. Raw [22] has even described a tumor in the right auricle which microscopically resembled a soft fibroma and which had caused metastases of similar structure in the liver.

In view of these considerations, the contention of Thorel that almost none of these endocardial masses is a neoplasm cannot be entertained, and the statement of Ribbert that they are all true tumors is probably closer to the truth.[23]

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21. Karrenstein: Ein Fall von Fibroelastomyxom des Herzens und Kasuistisches zur Frage der Herzgeschwülste besonders der Myxome, Virchows Arch. f. path. Anat. **194**:127, 1908.

22. Raw, N.: Brit. M. J. **2**:1335, 1898.

23. Debove: Bull. et mém. de la Soc. anat. de Paris, 1873. Reitman: Ztschr. f. Heilk., 1905, vol. 26. Djewitzki: Virchows Arch. f. path. Anat. **185**:14, 1906. Forel: Internat. Clin. **4**:147, 1919. Staffel, quoted by Kirch (footnote 16). Hagedorn: Centralbl. f. allg. Path. **19**:825, 1908. Simmonds: München. med. Wchnschr. **55**:1154, 1908. Steinhaus: Centralbl. f. allg. Path., 1899, vol. 10.

SUMMARY

A case is reported in which four distinct tumor nodules were found on the ventricular surface of a cusp of the pulmonary valve.

The tumors are considered to be true benign neoplasms, specifically hemangiofibromas.

A review of the literature indicates that most, if not all, of the tumor-like endocardial structures previously classed by some authors as pseudomyxomatous, organizing thrombi, as well as the valvular tumors, are true neoplasms.

Laboratory Methods and Technical Notes

A SIMPLE INEXPENSIVE PHOTOMICROGRAPHIC APPARATUS *

WILLIAM H. FELDMAN, D.V.M., M.Sc.
ROCHESTER, MINN.

Some one has said, in effect, that one picture is worth a thousand words. This is particularly apropos in the respective fields of biology, in which it is often desirable to supplement a written description by photographic illustrations. Because of the large investment necessary to secure photomicrographic outfits such as are catalogued by the various manufacturers, many who might in time become proficient in this fascinating branch of photography are denied the opportunity to try their hand at it. Although photography with a hand camera is so simple that even children may secure satisfactory results, photography with the aid of a microscope is for the majority clothed in a certain amount of mystery. As a consequence, many contributors to scientific literature either resort to drawings or, perhaps, omit illustrations which frequently would constitute the most valuable part of their publications. There are others who depend on a commercial photographer or a technician to supply photomicrographic illustrations. These illustrations are not always of the highest standard of excellence, and an otherwise meritorious contribution is often relegated to mediocrity because of abominations of the photographer's art.

To secure photomicrographs of excellent quality is not difficult when a relatively simple homemade apparatus is used, nor is it necessary for the average worker to have had extensive training in photography before satisfactory results can be obtained. Of course, knowledge of practical photography is helpful and should enable one to attain satisfactory results in a shorter time than would be possible without such experience.

Once mastered, photomicrography exerts continued fascination, and as a consequence, more and better pictures are obtained for the many purposes for which photographs are required to assist in telling the story or to complete records and files. After one has experienced the satisfaction of making photomicrographs, one would be reluctant to depend on another for this work.

* Submitted for publication, April 12, 1929.

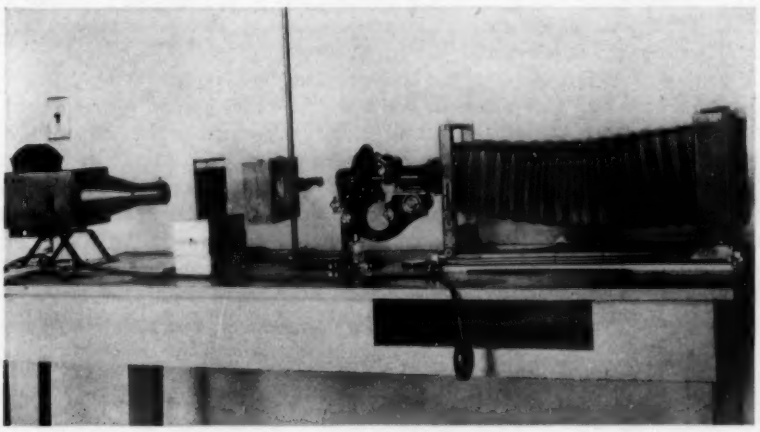
* From the Division of Experimental Surgery and Pathology, The Mayo Foundation.

THE APPARATUS

For nearly two years I have been making photomicrographs with an outfit which, with the exception of the microscope, was assembled from various odds and ends of laboratory equipment already available. A similar apparatus could probably be assembled at a total expenditure of $50 or less, and the results obtainable in work as a routine are comparable with those secured by the more complicated, expensive outfits.

The respective items used to assemble the outfit consisted of a microscope, a camera with a view of 5 to 7 inches, from which the lens and shutter were removed, two planoconvex condenser lenses suspended on a ring stand, a flat museum jar 5 by 4 by 0.75 inches to hold the liquid filter and a high power mazda microscopic lamp.

The apparatus should be assembled on a rigid table of such height as to render its manipulation convenient. The table should be approximately 24 inches wide and 5 feet and 6 inches long. The camera is first firmly attached to a one-half inch



The assembled outfit; the relative positions of the respective parts of the apparatus are shown.

pine board which will elevate it sufficiently to permit the operation of the pinion which controls the movement of the bellows forward and backward. By the use of "U" clamps, and bolts with wing nuts, the base of the camera is attached at one end of the table in the middle line. The microscope is mounted directly in front of the camera, the front portion of which may be adjusted to coincide with the height of the draw tube of the microscope when the instrument is in the horizontal position. If the lens and shutter are removed from the ordinary lens board, the opening is of a convenient size for the insertion of the objective of the microscope. It is not necessary that this union be tight; light can be excluded satisfactorily by wrapping a piece of black cloth around the draw tube just in front of the lens board. The microscope is held in place by a bolt which passes through the top of the table and through a piece of steel about 5 inches long and one fourth of an inch thick which is laid across both arms of the microscope stand. With a wing nut the instrument can be readily adjusted or removed if desired. At the other end of the table, at an approximate distance of 30 inches from the substage condensing lens of the microscope, the source of light should

be placed. I have had best success with a 400 watt, 110 volt mazda lamp, such as is available for dark-field illumination or other microscopic work. The style shown in the accompanying figure can be highly recommended. It is important that the camera, the microscope and the source of light be so adjusted as to be on the same plane and in exact alinement. Much adjusting is often necessary in order to achieve this result. At an approximate distance of 18 inches in front of the lamp the glass receptacle containing the ray filter should be placed. Although the base on which this rests should be rigid, the glass cell containing the filter should not be attached thereon, since it is important that this part of the equipment be readily removed while the adjustments preliminary to exposures are being made. Between the color filter and the microscope, two condensing lenses should be mounted as shown in the accompanying figure. The source of light should be controlled by a hand switch which obviates the necessity of a shutter in making exposures. After the equipment is assembled the light should be turned on and an attempt made to center an intense point of light from the condensing lens on the closed diaphragm of the microscope. In order to secure maximal illumination evenly over the exposed field it is imperative that all parts of the instrument be in perfect alinement, and this can be obtained only by careful preliminary adjustments.

When in use it is important that the apparatus be placed in a room free from vibrations of the floor. A basement room, with a concrete floor, serves admirably.

One of the most important features of this apparatus is the evenness of the source of light compared with the type of equipment in which the less constant, although more intense, arc light is used. After experience with both types of lights, it is my opinion that for average work as a routine the incandescent lamp operated on the ordinary A-C current is much to be preferred. Although the exposures are necessarily much longer when the incandescent bulb is used, the results obtained more than compensate for the added time required.

SUMMARY

A simple inexpensive photographic apparatus, which may be assembled from various items of equipment that are available in a laboratory and that may have been secured for other purposes, is described.

General Review

RECENT WORK ON THE EFFECTS OF INANITION AND MALNUTRITION ON GROWTH AND STRUCTURE

C. M. JACKSON, M.D.
MINNEAPOLIS

(Continued from page 1078)

EFFECTS OF A DEFICIENCY OF VITAMINS

First may be mentioned certain papers dealing with the effects of a deficiency of vitamins in general, either of a multiple shortage of the vitamins or of a shortage of vitamins complicated by a deficiency in other dietary factors.

Suzuki (1924) concluded that nephritis (or nephrosis) in the rabbit or in man may be caused either by infection or by toxic products arising from a disturbance of the intermediary metabolism through a deficiency of vitamins (or of similar substances). The principle of metabolic toxins was held to apply also to many other disorders, such as rickets, acute atrophy of the liver, pernicious anemia, Banti's disease and the leukemias. Abels (1924, 1925) pointed out that in avitaminosis (especially that due to a deficiency of vitamins B and C) the symptoms result from (*a*) dystrophy, or structural changes in the tissues; and (*b*) dysergy or lack of resistance of the tissues to infections. According to Cramer and Kingsbury (1924), a deficiency in vitamin A does not markedly affect the general humoral defenses of the body, but predisposes to infection through lesions in the local defenses, especially in the mucosae of the conjunctiva and of the respiratory and intestinal tracts. The importance of a deficiency of vitamins in reducing the resistance to infections was also recognized by Mellanby (1926), Eicholz and Kreitmaier (1928), Sherman and Burtis (1928) and many other investigators. The reason why a deficiency of vitamins (like inanition in general) reduces the resistance to infection is not entirely clear. Presumably the vitality of the cells and the tissues of the host is reduced relatively more than the vitality of the parasitic organisms. This theory is in agreement with observations indicating that the vitamin requirements for bacterial growth are somewhat different from those for the growth of the higher animals. The recent literature on this topic was reviewed by Uyei (1927).

Heaton (1926) showed by tissue cultures of chick embryos that the requirement for "growth hormones" or vitamins varies greatly among

the various tissues. In a solution of yeast, the cell growth of heart muscle was inhibited, while that of skin and intestine was not. The substance in yeast which promoted the epithelial growth was apparently the antineuritic vitamin B.

Since vitamins are essential to the normal growth of tissues, an imbalance or deficiency of vitamins may produce various abnormalities. Jorstad (1925) showed that the reaction of the subcutaneous connective tissue cells to coal tar in the white rat was modified by the presence or absence of vitamins A and B. The work of Fujimaki and Saiki in relation to carcinoma will be reviewed later in the discussion of vitamin A. Ludwig (1926) found that an inoculation of carcinoma usually failed in mice and rats on a vitamin-free diet, whereas it succeeded in normally fed controls. Erdmann, Haagen and Börnstein (1927) did not observe any visceral cancer in rats on diets with a low content of vitamin (similar to those used by Saiki); but they found two cases of subcutaneous adenocarcinoma (of mammary origin?) appearing in them. The authors believed that a deficiency of vitamins affects especially the reticulo-endothelial system. Erdmann and Haagen (1928) concluded that diets unbalanced in respect to vitamins favor the origin and development of tumors in rats.

Peller and Bass (1924) found the average weight of the human new-born less in the winter than in the summer. This they ascribed to a deficiency of vitamins in the maternal diet during the winter. Abels (1926) claimed that for the same reason the average weight of the newborn in Vienna was decreased during the winter after the war. Most authors, however, do not find a significant decrease in the average birthweight during the famine that was imposed by the war.

Glanzmann (1923) fed young rats for long periods on a vitamin-free diet of casein, starch, sugar, agar and salts. Growth was retarded, and finally a loss in weight occurred with marked atrophy of the liver and lymphoid tissues. The most striking change found in cell structure was an extensive nuclear pyknosis, which was ascribed to a disturbance in the colloidal conditions of the cell protoplasm. (In this connection Guggisberg's results, commented on in this paper under the head of deficiency of vitamin A, may also be referred to.) In rats on a similar vitamin-free diet, Stammers (1926) found marked loss in weight. Hypertrophy of the suprarenal glands was absent and little, if any, decrease occurred in the lipoid content of the cortex.

Henriksen (1925, 1925a) fed rats and guinea-pigs on a diet of oats and water (deficient in protein and salts, as well as in vitamins). He found extensive cell atrophy and degeneration in the liver, spleen, kidneys and suprarenal glands, as well as in the muscle and nervous tissues. The deficiency of vitamins, according to Henriksen, affects primarily the cell nuclei, probably through their component of bound fat. Spadolini

(1923) described an atrophic degeneration of the parathyroids in cats fed an avitaminic diet of autoclaved meat.

Banu and Heresco (1925) studied the effects of a multiple deficiency of vitamins on growth and bone structure in puppies. Junkersdorf and Jonen (1925) found serious retardation of development in puppies fed with a flour gruel that was deficient in protein as well as in vitamins. A peculiar disappearance of the pigment in the ball of the foot was noted. Groebbels (1923) likewise observed depigmentation in frog tadpoles (*Rana temporaria*) on a vitamin-free diet. Kopeć (1927) studied the effect of vitamin variation in the development of the moth, *Lymnantria dispar*.

That there is some undetermined dietary factor essential for the utilization of fat by the body was indicated by the work of Richardson (1925). She noted that when young rats were fed on certain apparently normal and balanced diets of highly purified foods, with the addition of the known vitamins, there was, nevertheless, in some cases a failure of growth with the frequent occurrence of greasy skin and hair.

General reviews of the results of previous work on the various vitamin deficiencies were given by McCollum and Simmonds (1925), Williams, McCarrison, Cramer and Findlay (1925), Doyle (1925a), Berg (1927), Stepp and György (1927) and Plimmer (1928). Parrino and Lepanto (1925) compared the effects (especially the changes in the blood) of simple inanition and of a deficiency of vitamins in pigeons and guinea-pigs. The relationship of a deficiency of vitamins to pediatrics was discussed by Reyher (1925). The anemia and urolithiasis produced by McCarrison (1927a, 1927b) with a variously deficient diet will be mentioned later.

Effects of a Deficiency of Vitamin A (Antixerotic).—Recent work confirms previous conclusions that deficiency of vitamin A prevents growth and development in the young and lowers resistance to infections (Cramer and Kingsbury, 1924; Sherman and MacLeod, 1924; 1925; Sherman and Burtis, 1928; Green and Mellanby, 1928). These infections are not specific for the ophthalmic tract as was formerly believed, but (as discovered by Mori) they involve also various other organs and systems. (The results reported by Bloch in 1924 may be brought into comparison here.) The local conditions in the corneal region (desiccation due to decreased lacrimal secretion) can scarcely account for the lesions in other organs. In many regions, a peculiar dystrophy of the epithelial cells appears, with a tendency to xerosis or hyperkeratosis, and possibly also malignant changes, as will be shown later.

The calf must now be added to the list of animals for which vitamin A is indispensable, as shown by Jones, Eckles and Palmer (1926). The typical symptoms of a deficiency of vitamin A appear in this species,

including the failure to grow, xerophthalmia, respiratory troubles, diarrhea and death. Recovery is possible on the addition of cod liver oil to the diet. Beard (1926) found that vitamin A is likewise necessary for the normal growth of the white mouse; but that the xerophthalmia does not appear to be characteristic for this species. According to Wolbach and Howe (1928), the ocular changes in the guinea-pig are also comparatively slight.

The effects of a deficiency of vitamin A will be grouped for convenience under the head of the various organs involved. The earlier literature on this subject was reviewed in my former work (Jackson, 1925).

Visual Apparatus: In young rabbits fed "bean curd dregs," Okamoto (1925) observed the development of rickets (due to a deficiency of vitamin D), and at a later period the typical symptoms of xerophthalmia, with corneal ulceration and perforation in extreme cases.

The experimental study of the characteristic ophthalmic disorder has been done chiefly on rats. Osborne, Mendel and Cannon (1924) noted ophthalmia appearing in about 60 per cent of 493 albino rats that for twenty days or more were on diets containing little, if any, vitamin A. Cases in which the ophthalmia failed to appear (likewise the negative results of Heijinian) were ascribed to a variation in the body's storage of the vitamin, or in the amount remaining in the incompletely purified diets. The age factor was emphasized by Sherman and Storms (1925). They found that the characteristic ophthalmia before death developed in three fourths of the rats placed at the age of 1 month on a diet deficient in vitamin A, but in only one fourth of those placed on the same diet at from 2 to 9 months of age. Mori (1922) described atrophic and degenerative changes in the epithelium of the lacrimal gland, associated with deficient lacrimal secretion and resulting in desiccation and keratomalacia. In the meibomian ducts, xerosis was observed, which sometimes caused occlusion and retention cysts. The lesions in the salivary glands and in the respiratory tract will be mentioned later.

Yudkin (1924, 1926) also made a careful histologic study of the visual apparatus at various stages of the typical disorder in young white rats. His results tend to confirm the theory that the condition of the eye is due primarily to the altered secretion of the paraocular glands, permitting bacterial infection. The disturbance appears more rapid and severe when the diet lacks another factor (such as phosphorus) in addition to vitamin A. Findlay (1925) found a decrease in the lysozyme content of the tears, which would increase the tendency of the eyes to infection during the deficiency of vitamin A.

A thorough study of the various organs of young albino rats on a diet deficient in vitamin A by Wolbach and Howe (1925a, 1925c, 1925d) revealed a characteristic involvement of the epithelial tissues far more

widespread than was observed by Mori. The glandular epithelium of the body in general underwent atrophy. In many regions, including the gland-ducts and mucous surfaces of the ocular, respiratory, alimentary and genito-urinary tracts, the epithelium presented focal proliferation with a pronounced tendency to keratinization in the superficial cells. Sometimes cysts and abscesses occurred. "In a few of our animals the behavior of the replacing epithelium in respect to numbers of mitotic figures and response on the part of the connective tissue and blood vessels suggests the acquisition of neoplastic properties. While the epitheliums which are the seats of these changes are largely of covering types, glandular epithelium is involved, specifically in the paraocular and salivary glands." Significant changes in the mitochondria were not found. The study of the visual apparatus included the eye, conjunctiva, cornea and glands (lacrimal, harderian, meibomian). The other organs will be mentioned later. Wolbach and Howe also studied the tissues from the fatal case in man reported by Wilson and DuBois (to be mentioned later). They found widespread keratinization similar to that occurring in the rat. The process of keratinization in the guinea-pig was also described in detail by Wolbach and Howe (1928).

The results reported by Mori and by Wolbach and Howe were confirmed by Manville (1925) and Freudenthal (1927, 1928) in experiments on rats. Manville concluded that the primary effect of a deficiency of vitamin A is a generalized decrease in glandular activity, resulting in xerosis of the eye and other regions (mouth, salivary glands, respiratory tract, skin), making possible a secondary bacterial invasion in these regions. Frontali (1926) also noted retarded growth and typical keratomalacia, together with infections of the urinary tract (to be mentioned later).

In rats subjected to diets deficient in vitamin A, Holm (1925) noted certain symptoms (enophthalmos, loss of hair at the ciliary edges, peculiar, reddish brown secretion) not appearing in human beings with the same disease. In individual rats much exposed to light, hemeralopia (day-blindness) could be demonstrated, as in man. This condition is perhaps to be explained by the further work of Fridericia and Holm (1925). They found that the visual purple was not affected by vitamin A starvation in darkness; but when the retina had been bleached by exposure to light, the regeneration of the visual purple was delayed in the test rats. This abnormality appeared much more pronounced in the albinos than in the pigmented (pied) rats, on account of the retinal pigment in the latter.

The results of recent studies of the effects of a deficiency of vitamin A in the human species are in close agreement with the results of the experiments on animals. Wilson and DuBois (1923) reported a detailed necropsy in a fatal case of keratomalacia in an infant fed for

three months on a dilution of condensed milk. A corneal ulcer had perforated nineteen days before death. The histologic results included inflammatory changes in the pancreas and in the lacrimal and salivary glands, and keratinization of the epithelium of the trachea, bronchi, uterine mucosa and pancreatic and submaxillary ducts. The desquamation of keratinized epithelium resulted in pancreatic cysts and bronchiectases. The ophthalmic changes were characteristic, as they were also in four cases reported by Wagner (1924) and one by Schwartz (1925).

Guiral (1924) described the symptoms in about sixty cases of keratomalacia in Cuban infants fed on milk from which the cream had been removed. There were conjunctivitis and deficient lacrimation. The cornea was sometimes apparently destroyed without visible pus or other bacterial complications. The feeding of orange juice caused a rapid recovery. Stransky (1924) presented six cases in infants, and Adamantiadis (1925) five cases of varied severity in malnourished children. Bloch (1924) described the ophthalmic lesions occurring in Danish children. Widmark (1924) reached similar conclusions, based chiefly on the work of the Danish ophthalmologist, Blegvad. According to this work, xerophthalmia is to be considered as, essentially, a general disturbance of nutrition, with a loss of resistance to infections. The disorder of the eye is only a partial symptom, appearing rather late. Corneal perforation may occur, resulting in blindness. In adults, the disorder is usually arrested at an early stage, associated with hemeralopia (meaning night-blindness; usually designated as nyctalopia). Abels (1927) stated that women are less susceptible to hemeralopia, on account of the greater amount of body fat with which the storage of vitamin is associated.

Harman (1925) described the disorder known as phlyctenular conjunctivitis, which among London school children ranks next to ophthalmia neonatorum as a cause of blindness from superficial inflammation. He concluded that the chief cause is malnutrition, but does not mention the possible relationship of this disorder to a deficiency of vitamin A.

By feeding the mothers on a modification of McCollum's rachitic diet (a mixture of corn meal, white flour, wheat bran, gelatin, calcium chloride and sodium chloride), von Szily and Eckstein (1923) produced, they said, cataract in the eyes of the nursing white rats. The rats were retarded in growth but did not show signs of rickets. In addition to being deficient in vitamin A (which was considered the most important), the diet was also lacking in fat and phosphorus. Stepp and Friedenwald (1924) and Stepp (1925) were unable to confirm this result, but von Szily and Eckstein (1925) ascribed this failure to the use of a different diet. They confirmed their original result by new experiments, and suggested the possibility of a new "anticataract vita-

min Z." Jess (1925), however, not only failed to confirm the results of von Szily and Eckstein, but found cataract occurring spontaneously to a variable degree in about one third of 150 white rats examined. It appeared to be hereditary in some families. This observation threw great doubt on the whole question of experimental cataract, which awaits further investigation.

Respiratory Tract: Among the effects of a deficiency of vitamin A in rats, Mori (1922) observed cornification of the laryngeal epithelium, which became thickened and infiltrated with pus cells. The xerosis gradually involved the trachea and became complicated by an inflammatory condition of the trachea and lungs, which in some cases terminated in bronchopneumonia. Sherman and MacLeod (1924, 1925) also emphasized the increased susceptibility to infection and especially the tendency to diseases of the lungs appearing in young adult rats. Manville (1925) mentioned the occurrence of xerosis in the larynx, and of pyogenic infections in the nasal sinuses, the middle ear and the lungs. Wolbach and Howe (1925a, 1925c, 1925d) found the process of hyperkeratosis, with transformation of various epithelia into the stratified squamous form, "practically constant in the upper respiratory tract, including the whole of the nasal passages, larynx, trachea and bronchi." The lungs show secondary changes, due chiefly to occlusion of the bronchi with desquamated keratinized cells, i.e., bronchiectases, with or without infection. They later (1928) described similar changes in guinea-pigs on diets deficient in vitamin A. Similar results were obtained in rats by Goldblatt and Benischek (1927). Respiratory troubles were mentioned also by Jones, Eckles and Palmer (1926) as one of the symptoms of a deficiency of vitamin A in calves.

Alimentary Tract: Gastro-intestinal disorders are common in many forms of malnutrition, including that due to a deficiency of vitamin A. Cramer (1923) held that one specific function of vitamin A is to maintain the integrity of the intestinal mucosa, thus preventing bacterial invasion. Guiral (1924) observed that infants on a diet of skimmed milk are likely to develop diarrhea in addition to keratomalacia. A watery diet is contra-indicated, because the associated deficiency in all vitamins intensifies the disorder. Diarrhea is also mentioned as one of the symptoms of a deficiency of vitamin A in young rabbits (Okamoto) and in calves (Jones, Eckles and Palmer).

Mori (1922) found normal cornification in the oral mucosa of rats on diets deficient in vitamin A. The salivary glands (parotid, submaxillary and sublingual), however, showed atrophic epithelium with deficient secretion. The epithelium of the salivary ducts often presented a remarkable degree of cornification and desquamation, occluding the lumen so as to form retention cysts and abscesses. Manville (1925) mentioned xerosis of the mouth, with oral, lingual and salivary

abscesses. Sherman and Munsell (1925) noted pus in one or more of the glands at the base of the tongue in 76 per cent of the cases. Wolbach and Howe (1925a, 1925c, 1925d) found the specific keratosis appearing in the salivary and accessory glands of the mouth and pharynx, and more rarely in the pancreas (especially in the ducts). Abscess-like cavities may occur, with yellowish, cheesy content from desquamated, keratinized epithelium. Goldblatt and Benischek (1927) observed similar lesions and emphasized especially the occurrence of abscesses at the base of the tongue. Fujimaki and others (1927) did not find any definite changes in the epithelium of the esophagus in test rats.

Lesions of the teeth were observed in albino rats deficient in vitamin A by Jackson (1925a). The incisor teeth appeared chalky-white, irregular and sometimes broken. The upper incisors were sometimes greatly elongated, failing to articulate with the lower. Wolbach and Howe (1925d) noted but few gross changes in the teeth of their test rats, although there was a variable atrophy of the odontoblasts and an irregular formation of dentine. Marshall (1927) observed attrition and abrasion of the tooth surface in both the test rats and the normal controls. Caries appeared in the adult test rats, but not in the younger ones. Lesions of the pulp, such as abscesses and calcification, were demonstrable in teeth that did not show caries as well as in those with caries. Although caries was apparently produced by the deficiency of vitamin A, it was not altered or arrested by a later addition of vitamin A to the diet.

Although Wolbach and Howe did not find any changes in the epithelial lining of the stomach and the intestines, they mentioned that the proliferative changes in other regions suggested the acquisition of neoplastic properties. Pappenheimer and Larimore (1923) observed gastric lesions in twenty of thirty-six rats on diets variously deficient. The addition of cod liver oil to a diet deficient in a fat-soluble vitamin afforded complete protection. Lesions were not found in forty-three rats on adequate diet. The lesions included an inflammatory edema of the mucosa and the submucosa, with a marked cellular reaction and localized ulceration. They occurred near the ridge at the junction of the fore-stomach and the glandular stomach. In a later study (1924), the gastric lesions were found in sixty-eight (61 per cent) of 112 rats on deficient diets, and in only five (7 per cent) of sixty-six controls; but an irritation by ingested hairs was thought to have been an important pathogenic factor.

Reference was made in a previous paragraph to the epithelial changes produced by Fujimaki and his associates (1927, 1927a) (Saiki 1927). The vitamin A deficient diet of casein, dextrin, olive oil, salt mixture and yeast was fed to young or adult rats for periods varying

from 58 to 318 days. The location and frequency of the most definite epithelial changes produced were summarized as follows:

TABLE 1.—*The Epithelial Changes Caused in Rats by a Diet Deficient in Vitamin A (as Observed by Fujimaki and His Co-Workers)*

Organs in Which Lesions Occurred	Number of Rats	Degrees of Hyperkeratosis and Atypical Epithelial Growth with Incidence of Each		
		Marked	Moderate	Slight or Absent
Fore-stomach	49	5 (10%)	12 (24%)	32 (66%)
Sublingual duct	29	7 (24%)	9 (31%)	13 (35%)
Bladder	30	3 (10%)	4 (13%)	23 (77%)
Renal pelvis	39	2 (5%)	2 (5%)	35 (90%)

Definite gastric changes thus appeared in about one third of the rats tested. The occurrence of papillomatous or carcinomatous lesions in the rats on diets deficient in vitamin A was previously reported by Fujimaki at meetings of the Japanese Pathological Society and the Fourth Congress of the Far Eastern Association of Tropical Medicine in 1925. The proliferative changes in the stomach apparently began with hyperkeratosis and epithelial growth unassociated with any local inflammatory reaction or preliminary ulceration. Along with the development of a heterotopic invasion of proliferated epithelia, a round cell infiltration in the mucosa and submucosa gradually became more distinct. The characteristic changes were not found in the cylindric epithelium of the glandular portion of the stomach, bile duct, uterus, trachea or bronchi. However, in one case a metastatic formation appeared in the lungs. The more negative results of Erdmann and her associates on diets of similarly low vitamin content were mentioned in a previous paragraph.

Possibly because the liver is normally rich in stored vitamin A (as shown by Wagner in 1924, and others), few observers have noted any results of a dietary deficiency of vitamin A in this organ, aside from moderate atrophy of the gland cells. Mori, Wolbach and Howe did not find any specific changes in the liver. Fujimaki (1926) and Saiki (1927), however, were able to produce biliary as well as urinary calculi. The concretions appeared in the bile ducts (the rat not having a gallbladder), and developed more readily when the diet was deficient in protein or phosphorus and calcium as well as in vitamin A.

Urinary System: The effects of a deficiency of vitamin A on the urinary system have been frequently demonstrated. Mori (1922), however, did not find any abnormality in the kidneys. One of the most significant and important of recent advances was the experimental production of lesions of the urinary tract, with formation of calculi, by means of the deficient diet.

An epidemic of nephritis was observed by Jackson (1925a) in a colony of albino rats fed on a cereal mixture apparently deficient in

vitamin A. The kidneys showed various stages of a focal interstitial nephritis, with round cell infiltrations. Some of the tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was ascribed to an infection made possible by the lowered resistance. When one nephritic kidney was removed, the other usually showed marked and progressive compensatory hypertrophy (up to 120 per cent), with a simultaneous decrease in body weight.

In seven young white rats that had died with xerophthalmia on diets deficient in vitamin A, Frontali (1926) likewise found constant infections of the urinary tract. Six of the seven showed multiple renal abscesses, either gross or microscopic, and the seventh had renal congestion and hemorrhages. The renal pelvis and ureter were also involved. All seven showed a variable degree of cystitis with submucous infiltration, epithelial desquamation, metaplasia of epidermic type and formation of corneous pearls.

In rats and guinea-pigs deficient in vitamin A Wolbach and Howe (1925a, 1925c, 1925d, 1928) likewise observed the characteristic epithelial keratosis in the renal pelvis, the bladder and the seminal vesicles, but not in the renal parenchyma. Fujimaki, Kimura, Wada and Shimada (1927, 1927a) (the results reported by Saiki in 1927 may also be consulted) similarly found hyperkeratosis and atypical epithelial proliferation in rats suffering from a chronic deficiency of vitamin A. As shown in the preceding paragraphs, the lesions were most distinct in the stomach and the sublingual duct, but in a smaller percentage of cases appeared also in the urinary bladder and the renal pelvis. Other epithelia showed little, if any, change.

Fujimaki (1926) and Saiki (1927) also investigated the occurrence of calculi in the urinary tract and the bile ducts in hundreds of albino rats on diets variously deficient. The concretions appeared sooner in the rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In six rats stone in the bladder (shown by x-rays) disappeared after the animals had been placed on a diet rich in vitamin A.

The experimental production of stone in the bladder (urolithiasis) was also accomplished by McCarrison (1927a, 1927b, 1927c, 1928), using an unbalanced cereal or flour diet (deficient in protein as well as in vitamin A and probably D), with or without excess of earthy phosphates. Of seventy-two young rats on the test diet for more than eight weeks, twenty-one (or 30 per cent) had stone in the bladder post mortem. The stones were small and single or multiple (up to five), and were mainly composed of earthy phosphates. Eighteen of the twenty-one with stone showed also variable degrees of cystitis, and in eight cases one ureter was distended with pyonephrosis or hydro-

nephrosis. Stones were not found in 340 normal rats on the stock diet. The addition of milk to the cereal diet invariably prevented the formation of the calculi.

Van Leersum (1927, 1927a, 1928, 1928a) also produced phosphatic calculi, sometimes demonstrable by x-rays, in the ureter and urinary bladder in rats on standard diets deficient in vitamin A. Of 645 test rats, 197 (35.4 per cent) had calculi; forty-six showed, in addition, hematuria. Calculosis was found much more frequently in the male than in the female rats. Cystitis was not observed. In 88 per cent of the test animals examined, sections of the kidney showed also numerous small calcareo-fatty granular concretions or casts in the tubules and ducts. He believed that morbid changes in the epithelium of the renal tubules caused the calcareous deposits, and that these became liberated and grew to form larger concretions in the bladder. Perlmann and Weber (1928) similarly obtained bladder stones in rats. Hughes (1928), however, did not find urinary or biliary calculi resulting from a deficiency of vitamin A in hogs; but in chickens he observed heavy deposits of urates throughout the body.

Blood: Cramer's theory (1923) that the blood platelets are reduced in number by a deficiency of vitamin A has not been confirmed by more recent work. Stammers (1925) did not find any significant change in the platelet count. Falconer and Peachy obtained an average reduction of 204,209 in twenty-four platelet counts on test rats, but concluded that the change was not sufficiently striking or constant to be held specific. They also found a slight increase in the number of red cells; and some leukocytosis with an inversion of the polymorphonuclear-lymphocyte ratio, which they ascribed to the frequent presence of low grade infections. In a case of keratomalacia in an infant Schwartz (1925) made a blood count of 4,800,000 red cells, and 13,500 leukocytes (78 per cent of which were polymorphonuclears and 22 per cent lymphocytes).

As a result of extensive dietary experiments on white rats, Koessler, Maurer and Loughlin (1926) concluded that vitamin A is necessary for the normal regeneration of blood, and that its absence produces a condition similar to pernicious anemia. McCarrison (1927a, 1927b) similarly found (in addition to urolithiasis) a condition resembling pernicious anemia in rats on defective diets, deficient in protein as well as in vitamin A.

Reproductive Tract: In many of the studies to be mentioned here, a deficiency of vitamin E (mostly unrecognized) probably complicated the effects of the deficiency of vitamin A. Yamasaki (1923) fed sixty adult white mice a basal ration of casein and polished rice, plus additions to make a normal (complete) diet in one group and variously deficient diets in other groups as follows: group 1, a diet deficient in salt; group

2, a diet deficient in vitamin A; group 3, a diet deficient in vitamins B and C; group 4, a vitamin-free diet; and group 5, a diet of water only. Some died on the deficient diets; others were killed in three weeks. In all the test groups, characteristic changes appeared in the gonads—a disturbance of spermatogenesis in the testis and follicular atrophy in the ovary. The ovary in some individual cases showed an apparent increase in the stroma and the interstitial gland cells. The testis presented a variable amount of degeneration in the seminiferous epithelium, but with little change in the interstitial gland cells. Giant cells appeared in the seminiferous tubules in all the test groups excepting those on water only. In general, the changes were greatest in the mice dying after the longest periods. Those in group 2 (on the diet deficient in vitamin A) showed gonadal changes similar to the changes observed in group 3; somewhat more extensive than the changes found in group 1, but less than those observed in groups 4 and 5.

The remaining studies were chiefly on the rat (the species unfortunately was not stated in some cases). Sherman and MacLeod (1925) fed rats on a diet containing too little of vitamin A, which permitted growth to nearly average adult size, but usually resulted in sterility. Parkes and Drummond (1926) found that rats on a diet deficient in vitamin A were dwarfed, weighing from 70 to 90 Gm. at from three to five months, and were sterile. Histologic examination did not reveal any reason for this sterility. "Gametogenesis was found to be in progress in these stunted animals, and the accessory organs appeared to be normal." Vaginal smears showed estrual cycles in the females. Since the test rats failed to copulate with each other or with normal rats, it was concluded that their sterility was due primarily to physiologic debility. With recovery of normal weight by the rats, on natural diets, breeding and fertility were restored. Stone (1925), on the contrary, did not find any significant decrease in the copulative ability of male rats on diets deficient in vitamins A and B; but these rats were apparently less severely stunted in growth. They showed, nevertheless, a retardation in spermatogenesis and in the development of the accessory reproductive apparatus.

Guggisberg (1925) fed rats from the eighteenth day of age on Glanzmann's diets, vitamin-free or deficient in vitamin A. Growth was greatly retarded for from seventy to ninety days, with imperfect development of most of the organs, especially of the reproductive tract. The ovaries were small, with immature follicles; the uterus small with thin walls. The testes also were hypoplastic. Spermatozoa were rarely matured, although the interstitial cells were well devoloped. Pregnancies (which were rare) usually resulted in abortion or weakly developed young. In general, the effects on the testis were much greater than those on the ovary. Likewise, the results of a vitamin-free diet were more marked than those of a diet deficient in vitamin A alone.

Simonnet (1925) likewise found a difference between the sexes in the effects of a deficiency of vitamin A on the gonads of rats. With retarded general growth, the weights of the testis were markedly subnormal, while the weights of the ovary appeared more nearly normal. The atrophy of the testis was also much greater than that resulting from simple underfeeding. The rats on diets deficient in vitamin A were sterile, but fecundity was restored on refeeding with a complete diet. The possibility of an antisterility vitamin E was recognized. Goldblatt and Benischek (1927) also mentioned atrophy and degeneration of the epithelium in the tubules of the testis.

According to Fujimaki and his associates (1927), the epithelial hyperkeratosis characteristic of a deficiency of vitamin A is slight or absent in the uterus and vagina of the rat. Wolbach and Howe (1925d), on the contrary, noted the occurrence of keratinization in the uterus and oviducts, as well as in the epididymis, prostate and seminal vesicles of the rat. The process began in the uterine glands as well as in the uterine lining epithelium, which became stratified and keratinized. They (1928) found the keratinization of the uterine epithelium much greater in the guinea-pig than in the rat.

As Light (1927) pointed out, this characteristic keratosis of the epithelium (rather than any ovarian disturbance) probably caused the typical continuous appearance of cornified epithelial cells in the vaginal smears of female rats on diets deficient in vitamin A. Evans (1928) noted that although estrum and ovulation may continue in rats on a diet deficient in vitamin A, only one fifth of the copulations lead to the birth of litters. The cornified cells in the vaginal smears continue throughout gestation. Bishop, Scott and Morgan (1928) observed multiple uterine deciduomas occurring in a rat on a diet containing too little vitamin A.

Suprarenal Gland: Plaut (1923) confirmed the occurrence of a hypertrophy of the suprarenal glands in avitaminosis. In four control rats, the suprarenal glands formed 0.25 per cent of the weight; in four on diets lacking in vitamin A, the suprarenal glands contributed 0.4 per cent of the weight; in four on a diet deficient in vitamin B, the glands totaled 0.6 per cent, and in two on a diet deficient in all the vitamins, the suprarenal glands made up 0.8 per cent. Hemorrhages were not noted in either the cortex or the medulla. Wolbach and Howe (1925d) did not find any gross or histologic changes in the suprarenal glands of rats on diets lacking in vitamin A. In young rabbits, with experimental xerophthalmia, Okamoto (1925) noted enlargement of the suprarenal glands, with thickening of the cortex. Kolliner (1927) observed the nucleus-plasma ratio in the suprarenal cortex and medulla of rats on variously deficient diets (wheat plus various additions), but did not reach a definite conclusion as to the results.

Miscellaneous Organs: Wolbach and Howe (1925a, 1925c) noted, among other changes, a marked atrophy of the epithelial tissues in the thyroid, parathyroid and pituitary glands of rats with experimental xerophthalmia. However, they failed (1928) to find this atrophy in tests on guinea-pigs. Plaut (1923) found in rats with avitaminosis an atrophy of the parathyroids and a decrease in the fat content of the parathyroids. He also noted abundant sudanophil fat in the spleens of rats on diets lacking in vitamin A but not in those of rats on diets deficient in vitamin B. The splenic megakaryocytes disappeared, as was observed by Wolbach and Howe (1925d).

One might expect the hyperkeratosis described by Wolbach and Howe and others as a specific effect of a deficiency of vitamin A to be most definitely manifested in the epidermis. But this apparently does not occur. Manville mentioned a xerosis of the skin; but Wolbach and Howe and Fujimaki and Saiki found little, if any change (aside from atrophy). Frontali (1926) noted multiple small cutaneous abscesses in two of seven young rats with xerophthalmia from a diet deficient in vitamin A. Portman (1927) found a general atrophy of the skin (excepting the stratum corneum) in rats with a deficiency of vitamin A; similar observations were made with regard to a deficiency of vitamin B and to general underfeeding.

Hayashi (1924c) did not find any appreciable changes in the skeletal muscle and peripheral nerves of rats with a deficiency of vitamin A. This is in agreement with the results of Wolbach and Howe (1925d). Hughes and Leinhardt (1928), however, reported nervous symptoms (incoordination, spasms, blindness) in pigs on diets deficient in vitamin A. A degeneration of the peripheral nerve fibers was demonstrated. Atrophic changes in the bone-marrow and the thymus of the guinea-pig were also noted by Wolbach and Howe (1925d). In some cases, the thymic (Hassall's) corpuscles were greatly enlarged and were cyst-like, filled apparently with desquamated, keratinized cells.

The rachitic changes found by Davis (1923) in the skeletons of puppies on rations deficient in vitamin A were doubtless due chiefly to an associated deficiency of vitamin D. On the other hand, the changes observed by Pappenheimer and Dunn (1925) in the "leg weakness" of chicks on a diet of maize and skimmed milk were apparently not rachitic. The skeletal lesions—arrested osteogenesis, osteoporosis and fibromyxomatous transformation of the marrow—point rather to a deficiecny of vitamin A. The disorder was prevented or cured by the addition of cod liver oil to the diet.

According to Freudenthal (1927, 1928), the changes in the region of endochondral ossification in young rats suffering from a deficiency of vitamin A include a general inhibition of the process of osteogenesis.

Effects of a Deficiency of Vitamin B (Antineuritic).—Evidence has been steadily accumulating that what heretofore has ordinarily been termed vitamin B is composite in nature. In addition to the well known antineuritic vitamin, there is in yeast at least one other distinct and separable component, sometimes termed the "growth promoting factor," which will be more fully discussed under the head "Recently Discovered Vitamins." However, most of the work up to the present on the effects of a deficiency of vitamin B has involved both factors, and the exact effects of the deficiency of the antineuritic vitamin alone are therefore still uncertain.

To the earlier work indicating that vitamin B (including both factors) is indispensable for growth may now be added the observations of Osborne and Mendel (1924a, 1925) Reader and Drummond (1926), Sure (1927, 1927a) and Moore, Brodie and Hope (1927) for the rat; Beard (1926) for the mouse; Utsumi (1924) for the chick, and Bechdel, Eckles and Palmer (1926) for the calf. Aron and Gralka (1925) added evidence that in growing rats vitamin B is not stored to any appreciable extent; and, according to Sure, this is especially evident when the lactating mother has been subjected to a deficiency of vitamin B. Clementi (1924) found that adult albino rats on a diet of polished rice (mixed deficiency) underwent a loss of weight, while the young showed arrested growth and nervous symptoms of the spastic-paretic type. Guest, Nelson, Parks and Fulmer (1926), Moore, Brodie and Hope (1927), Sure (1924a, 1927), Mottram (1928) and others showed that the amount of vitamin B necessary for normal lactation is much greater than that required for normal growth and reproduction in the rat. Evans and Burr (1928) demonstrated that the increased requirement during lactation is for the antineuritic rather than the "growth promoting" vitamin B factor, and that about five times the usual intake is required during the latter half of the lactating period.

Frank (1923) noted that in young rats on fatty diets rich in vitamin A, and deficient in B and C, the skin may present an eruption, similar to that in the exudative diathesis of infants. Ishido (1922) noted a delay in the healing of skin wounds in rats and guinea-pigs on diets deficient in vitamin B and vitamin C, respectively. Frog tadpoles (*Hyla septentrionalis*) on a diet of white bread (mixed deficiency) developed paralyses, muscle degeneration, cardiac dilatation, edema, joint lesions and peritoneal hemorrhages, as observed by Hoffmann (1926). In this case, as in the monkeys fed only on polished rice by Paffrath and Schlossman (1926), one may be dealing with a mixture of beriberi and scurvy. The same possibility is to be suspected in the case of hemorrhagic disorder of the new-born described by Moore and Brodie (1927). Moore, Brodie and Hope (1927), however, produced in young rats on a diet deficient in vitamin B conspicuous subcutaneous, visceral and intracranial hemorrhages (both macroscopic and micro-

scopic), in addition to the usual paralysis and degeneration of the peripheral nerves. Similarly, Sure and Schilling (1928) noted hemorrhages especially constant and conspicuous in the bones of the young rats (which were not susceptible to scurvy).

The mechanism of the pathogenesis in beriberi in man and experimental polyneuritis still remains uncertain. Ogata (1920) supported the view that the "rice disease" (polyneuritis gallinarum) is a disturbance of carbohydrate metabolism, caused by a lack of the antineuritic vitamin B. Riquier (1925) held that the disturbance involves metabolism in general and not merely that of carbohydrates, and that it results in toxic products which injure the various tissues and organs, thereby causing the characteristic phenomena of the disorder. Wetzel (1924), as did earlier observers, found the loss of weight in pigeons on a diet of polished rice similar to that in complete starvation. Drummond and Marrian (1926) likewise concluded that the failure of nutrition in rats lacking in vitamin B is essentially the same as in simple starvation. Kon and Drummond (1927), feeding the same amount of food to control pigeons as was consumed by those on diets deficient in vitamin B, did not find evidence that this vitamin controls carbohydrate metabolism. While the acute nervous symptoms appeared only with a deficiency of vitamin B, these symptoms could not be attributed to the degenerative changes in the nerves, which occurred also in the control group. Their conclusion, in agreement with that of Ogata and his co-workers (1924a), is that existing theories do not satisfactorily explain the rôle of vitamin B in the organism. Plimmer and his associates (1927) suggested that vitamin B is a constituent of the cell nucleus and is therefore involved in all cell growth and maintenance.

Graeff (1925) concluded that in beriberi in man the clinical and anatomic data indicate the primary importance of the changes in nerves and muscles (perhaps including those in the muscle of the arteries and the gastro-intestinal canal) together with the dilatation of the right side of the heart. The venous stasis following the cardiac dilatation causes the edema and secondary changes in the various organs. Yet, in experiments on animals, the nervous symptoms and changes are apparently not proportional to the deficiency of vitamin B. Graeff therefore believed that some infectious agent, as well as the deficiency of vitamin, may be a factor in the pathogenesis of beriberi.

Ogata and his associates (1921, 1923, 1924, 1924a) vigorously opposed the doctrine that beriberi in man is identical with the experimental B avitaminosis (polyneuritis avium), emphasizing the differences between the two disorders, as summarized in the accompaning table.

On the other hand, Murata (1923) concluded that the disorder in rice-fed rabbits is essentially identical with beriberi in man, in etiology,

pathology and clinical phenomena. Minor discrepancies he ascribed to the difference in species. McCarrison and Norris (1924) and McCarrison (1928) likewise concluded that the basal factor in causing beriberi in man in India is a diet deficient in vitamin B. Experiments on pigeons, however, indicated that there is also an associated unknown agent specifically affecting the heart. Hayashi's (1924a) comparison of "polished rice disease" in the rat with beriberi in man was inaccessible.

Kepler (1925) described a case of typical beriberi in a negro woman of Philadelphia. She had lived over a year on a diet consisting chiefly of raw starch. Prompt recovery followed the addition of yeast to the diet. Scott and Herrmann (1928) found many cases among the rice farmers of Louisiana. Hoobler described the symptoms of a deficiency of vitamin B in children.

TABLE 2.—*Differences Between Beriberi in Man and Experimental B Avitaminosis (Ogata)*

Points of Comparison	Beriberi in Men	Deficiency of Vitamin B in Birds
Content of vitamin B in organs	Unchanged	Decreased
Nervous symptoms	Appear early in disease	Appear late in disease
Pulse rate	Increased	Not increased; slower toward end
Cardiac hypertrophy	Present	Absent (heart usually contracted)
Edema	Always present	Occasionally present
Edema in body cavities	Frequent	Occasionally present
Dyspnea	Present (respiratory paralysis)	Absent
Digestive disturbances	Slight	More severe
Red cells and hemoglobin content	Changes not marked	Distinctly decreased
Lymphopenia	Absent (sometimes lymphocytosis)	Marked and characteristic
Hemorrhagic diathesis	Absent	Present
Fever	Slight	Absent
Suprarenal glands	Medulla hypertrophied; chrome reaction increased	Cortex hypertrophied; medulla normal
Gonads (testis)	Changes not marked	Atrophy; decreased spermatogenesis
Resistance to infection	Sometimes dysentery and typhoid complications	Marked predisposition to septicemia and other infections

Grey (1928) concluded that in Japan the predominant rice diet results in a widespread "preberiberi" chronic condition, involving various factors as well as the deficiency of vitamin B. From experiments on pigeons, Grey (1928a) attributed the action of the vitamin B complex to two factors: a factor regulating oxidation in metabolism; and a factor maintaining the integrity of the tissues. In the absence of the latter, the tissues tend to degenerate in the following order: endothelial or epithelial, glandular, plain muscle, skeletal and nervous. Wenckebach (1928) believed that the retention of water, affecting particularly the nervous and muscular tissues, is the fundamental factor in the pathogenesis of beriberi.

Nervous System: Nearly all investigators find degenerative changes in the peripheral nervous system accompanying a deficiency of vitamin B, but they do not all agree as to the extent and significance of such

changes. The degenerative lesions in the peripheral nerves resemble those of a simple toxic (noninflammatory) peripheral neuritis, as found resulting from a polished rice (or other B-deficient) diet by Segawa (1914) in chickens and pigeons, by Lhermitte (1916) in young chicks, by Murata (1923) in rabbits and by Kingery and Kingery (1925) and Moore, Brodie and Hope (1927) in albino rats. However, Kon and Drummond (1927) did not find in pigeons any correlation between the neural degenerative changes and the acute nervous symptoms, and this corresponds with the experience of various other investigators. Riquier (1925) and Culley (1927), on the other hand, insisted that there is in polyneuritis gallinarum a general correspondence (in time and severity) between the neural symptoms and the degenerative changes. Both investigators agreed that the changes are not identical with those in typical Wallerian degeneration. Culley found that the primary lesion is in the axone, while Riquier believed it to be in the medullary sheath. Riquier, who made an unusually extensive and careful study of the changes in the entire nervous system of the pigeon, found the primary lesion in the peripheral nerves, but variably distributed. The sciatic nerve (the only one observed by some investigators) may be, he thought, but slightly affected, while other nerves (brachial and cervical) show severe lesions. Except in the vagus, the changes in the cranial nerves are slight. Different levels of the nerve trunks may be affected, but chiefly the distal regions. There are also variations according to the variety and the age of the pigeon and the stage of the disease. Riquier observed an absence of changes in the motor nerve endings. Woolard (1927), however, recently described changes in both the motor and the sensory nerve endings of the rat in starvation as well as in beriberi.

Scott and Herrmann (1928) concluded that the symptoms of beriberi in man are attributable to peripheral nerve (including vagus) degeneration, with secondary myocardial dysfunction. Hypertrophy of the right ventricle during beriberi has frequently been ascribed to obstruction of the lesser circulation, associated with paralysis of the diaphragm due to degeneration of the phrenic nerve. Ukai (1920), however, did not find any constant relation between degeneration of the phrenic nerve and cardiac hypertrophy in beriberi in man.

Riquier (1925) did not see any significant changes in the spinal ganglions of polyneuritic pigeons he employed (Nissl's method); but Spadolini (1922) found marked lesions in these ganglions in cats, as did also Kingery and Kingery (1925) in the spinal ganglions of rats. Ma (1925, 1925a) also described the occurrence, in beriberi in fowls, of a granular disintegration of the mitochondria in the spinal ganglion cells, probably associated with changes in the Nissl bodies.

Riquier did not find any constant or important changes in the sympathetic ganglions of polyneuritic pigeons, by Nissl's or Cajal's methods, a result confirmed by Woolard for the rat. Kingery and Kingery, however, described marked degenerative changes in the sympathetic ganglion cells of the rat (Nissl's method).

The changes in the central nervous system during beriberi (polyneuritis) appear to be variable. Richter (1913) noted a marked hyperemia with extravasations and progressive degeneration of the nerve cells in pigeons. Segawa (1914) observed degeneration especially in the cells of the anterior horn of the spinal cord. Lhermitte (1916) did not find any definite change in the spinal cord in the chick, studied by the Nissl method, but marked chromatolysis and proliferation of neuroglia cells in the cortex of the brain. Kihn (1922), in addition to vacuolation and chromatolysis of the nerve cells, found congestion, edema and multiple hemorrhages of variable size in various parts of the brain in pigeons and rats. In the rabbits observed by Murata (1913), the brain appeared subnormal in weight. Kingery and Kingery (1925) described degenerative changes in Purkinje's cells in rats, but Woolard (1927) did not find any abnormality in the central nervous system. Riquier (1925) similarly concluded that in the pigeon changes in the brain cells are relatively slight and of secondary importance. According to Grey (1928a), the neural symptoms arise late during the "polished rice disease" in pigeons, and are ascribed to irritation of the nerve cells through lymph congestion or hemorrhage in the central nervous system.

Musculature: In polyneuritic chickens and pigeons, Segawa (1914) found degeneration of the skeletal muscle, which was considered as secondary to the lesions of the peripheral nerves. In experimental beriberi of rabbits, Murata (1923) observed gross atrophy of the muscles, especially in the hind limbs. Occasional small grayish spots showed (on microscopic examination) the so-called waxy Zenker's degeneration which occurs in beriberi in man. Atrophy of the muscle fibers appeared, with nuclear proliferation. There was also a variable interstitial fibrosis with leukocytic infiltration, and sometimes fatty metamorphosis or edema. The respiratory muscles (diaphragm, intercostals) in general were less affected than the peroneal. The degenerative lesions rarely appeared in animals dying without symptoms of beriberi. On the other hand, in beriberi in pigeons, Riquier (1925) usually found merely simple atrophy of the fibers in the muscles of limbs and trunk, these muscles being greatly reduced in volume. A few fibers showed homogeneous structure, loss of striation and doubtful nuclear proliferation. Some fibers showed rows of sudanophil droplets. Tamura (1924) found in chickens either starved or on a diet of polished rice, a great decrease in the fat content of the muscles;

but a tendency toward increase in the cholesterol content. In beriberi in man, Pons and Lalung-Bonnaire (1927) observed the successive involvement of the diaphragmatic, inferior costal, superior costal and pectoral musculature, resulting in respiratory paralysis.

Heart and Blood Vessels: The changes in the heart in beriberi have been much disputed. Cardiac hypertrophy (of the right ventricle) secondary to respiratory (circulatory) obstruction, has been found characteristic of beriberi in man (Aalsmeer and Wenckebach, 1928), in contrast with the cardiac atrophy usually noted in the experimental polyneuritis of animals (Ogata and his co-workers, 1923 and 1924). In some cases, cardiac distention (which frequently occurs in the atrophic hearts) was apparently confused with cardiac hypertrophy. Segawa (1914) noted dilatation of both ventricles in polyneuritic chickens and pigeons. He thought that a toxic myocardial degeneration caused the cardiac insufficiency resulting in general venous stasis. Ogata (1920) found that, even though loss in weight was prevented by forced feeding of the test chickens and pigeons, there was myocardial atrophy with a decrease in the weight of the heart. Riquier (1925) observed a weakening and distention of the heart in pigeons, although but slight degenerative changes appeared in the cardiac muscle. Shiga (1926) asserted that he had seen cardiac hypertrophy in monkeys on a diet of polished rice. McCarrison and Norris (1924) and McCarrison (1928) concluded that even in pigeons there are different types of the disorder, including polyneuritis (in the absence of vitamin B) with cardiac atrophy, and beriberi, caused by a deficiency of vitamin B, with the presence of some unknown associated factor producing cardiac hypertrophy. Plimmer and his associates (1927) mentioned a frequent cardiac enlargement in birds, especially chickens, with chronic deficiency of vitamin B.

Kure assumed that the cardiac hypertrophy in beriberi in man is the result of respiratory paralysis, and produced (according to the record) a similar effect in the rabbit by section of the phrenic nerve. In beriberi in man, however, Ukai (1920) found that the hypertrophy of the right ventricle is not always accompanied by phrenic degeneration. Murata (1923) demonstrated that in beriberi in rice-fed rabbits the weight of even the distended heart (including blood) remains nearly stationary, while that of the empty heart averages 34 per cent below normal. The separate weights of the atria and of the right and left ventricles show slight changes. Sundararajan (1928) statistically demonstrated the cardiac atrophy in McCarrison's polyneuritic pigeons.

Moore and Brodie (1927) noted hypertrophy and dilatation of the right ventricle in a case of infantile beriberi. A series of studies on beriberi in man in Cochin-China recently appeared. Bablet and his co-workers (1927) described the radioscopic appearance in the cardiac

enlargement and displacement. Death is usually caused by the cardiac or cardiorespiratory disturbance. Pons and his associates (1927) described the clinical cardiac and respiratory phenomena. The cardiac injury, according to them, is reflected in the lung; and the respiratory condition in turn reacts on the weakened heart. Bernard and others (1927) concluded that cardiac insufficiency and capillary alterations are extrarenal factors in producing the edema of beriberi in man. Hydropericardium is a characteristic phenomenon, both in beriberi in man (Bernard and his associates) and in experimental polyneuritis (Segawa, 1914). As has been noted, Scott and Herrmann (1928) emphasized the importance of the cardiac lesions in beriberi in man. Mebius (1928) described a primary hydropic degeneration of the cardiac muscle in beriberi in man.

A fatty degeneration of the smallest arterioles and of the capillaries, but not of the larger vessels, was observed by Alpern (1923) in the wings of pigeons on a diet of autoclaved rice. These changes were not found in complete starvation. Fatty degeneration in the media of the small arteries of polyneuritic birds was noted also by Segawa (1914). As has been mentioned, hemorrhages in beriberi have been found by various investigators.

Stomach and Intestines: Ogata (1920) found relatively slight changes, including atrophy and catarrh of the mucosa, in the gastro-intestinal wall of rice-fed chickens and pigeons. Nevertheless, Ogata and his associates concluded that more severe digestive disturbance is one of the diagnostic features distinguishing experimental polyneuritis of animals from beriberi in man. Moore and Brodie (1927) observed merely hyperemia of the stomach and duodenum in their case of infantile beriberi. Scott and Herrmann found the gastro-intestinal symptoms vague and inconstant. Atrophic and degenerative changes in the gastro-intestinal mucosa of cats on a diet of autoclaved meat (deficient in vitamins B and C) were noted by Spadolini (1922). Somewhat similar though relatively slight changes (chiefly secondary to the venous stasis?) were described by Murata (1923) as occurring in rabbits, and by Riquier (1925) as occurring in pigeons. Carra (1925) and Guarino (1927) found the gastro-intestinal lesions in polyneuritic pigeons similar to those in scorbutic guinea-pigs. Plimmer and his associates (1927) observed abundant abdominal fat and frequent intestinal stasis in birds (chickens, ducks, pigeons) during chronic deficiency of vitamin B. Gastric atony and distention were noted by Rowlands and Browning (1928) in rats on diets short of vitamin B. The involvement of the digestive tract is doubtless largely responsible for the general malnutrition which is so frequent in inanition due to deficiency of vitamin B and other partial dietary deficiencies, especially in the later stages.

Larimore (1928) found that chronic ulcerative colitis in man is greatly relieved by diets rich in vitamins, especially vitamin B.

Liver: Ogata (1920) noted that in voluntary feeding of chickens on polished rice there was a marked atrophy of the liver, associated with loss in body weight, which he ascribed to simple inanition; whereas during forced feeding of rice there was a striking hypertrophy of the liver (from 50 to 80 per cent), associated with fatty infiltration, although the weight of the body increased only 4.5 per cent. In pigeons, with forced feeding of rice, there was an average loss of 12 per cent in the weight of the body, with but little change in the weight of the liver. Lopez-Lomba and Randoin (1923) found a loss of from 30 to 35 per cent in the weight of the body and of 45 per cent in the weight of the liver in pigeons on a diet deficient in vitamin B. McCarrison and Norris (1924) observed enlargement of the liver in one type of beriberi columbarum. In rice-fed pigeons, Riquier (1925) observed marked and uniform hepatic congestion, with bile vessels also dilated, atrophy of the parenchyma, with slight amounts of fat and glycogen, and, rarely, small hemorrhages or round cell infiltration. Carra (1925) noted moderate fatty infiltration of the liver cells in beriberi in pigeons. In rice-fed rabbits, Murata (1923) found a marked loss in the weight of the body and that of the liver. The liver grossly appeared paler and browner. Microsopically, fatty deposits in the gland cells and Kupffer cells were nearly constant, and doubtless were associated with the hypercholesteremia that occurs during the feeding of rice (Umehara). Hemosiderin deposits occurred in one third of the cases; more rarely fibrosis (cirrhosis), with variable round cell infiltration. Yoshida (1924) likewise noted fatty infiltration and variable interlobular fibrosis and leukocytic infiltration in the liver in rabbits (more rarely in guinea-pigs) fed on boiled rice. In a case of infantile beriberi, Moore and Brodie (1927) observed cloudy swelling, vacuolation and deposit of pigment in the liver cells.

Pancreas: Ogata (1920) found an atrophy of the pancreas to half its original weight in rice-fed pigeons. The decrease was relatively less in chickens. The acini appeared atrophic, except near the pancreatic islets, where they were filled with zymogen granules (this observation confirming Segawa's). The islets became greatly increased in size and in number (fivefold per millimeter in chickens; fourteenfold in pigeons), developing out of the centro-acinar cells. Similar results were obtained by Ogata, Kawakita, Oka and Kagoshima (1921). Lopez-Lomba and Randoin (1923) reported a decrease of 24 per cent in the weight of the pancreas in beriberi in pigeons. Artom (1923) claimed that the pancreas in rice-fed pigeons differs from that in starved pigeons in that there is an increase in zymogen granules and a distention of some of the tubules through a retention of secretion. In rice-fed rabbits,

Murata (1923) found a marked loss in weight of the pancreas, with atrophy of the acini, but neither hypertrophy nor hyperplasia of the islets of Langerhans. Hoshi und Ukai (1926) likewise failed to see evidence of such changes in the pancreatic islets in fowls on a diet of polished rice. Riquier (1925) and Bierry and Kollmann (1927), on the other hand, confirming the observations of Ogata, found an increase in the number and the volume of the pancreatic islets in polyneuritic pigeons.

Kidney: Ogata (1920) demonstrated a marked increase in the weight of the kidney in rice-fed birds, the hypertrophy averaging 34 per cent in pigeons and from 20 to 43 per cent in chickens. The increased weight was associated with a (toxic?) nephritis. Leukocytic infiltration and tubular degeneration appeared in the affected renal areas, although the glomeruli were normal. Lopez-Lomba and Randoin (1923) found a smaller increase (about 10 per cent) in the weight of the kidney in pigeons on a special diet deficient in vitamin B. Murata (1923), on the other hand, noted an apparent average loss of about 9 per cent in the weight of the kidney in twenty rabbits with beriberi. The epithelium of the convoluted tubules appeared atrophic, without degeneration or necrosis. The glomeruli were normal. Cellular infiltration or changes were not observed in the interstitial tissue. Hyaline cylinders and cystic dilatations often occurred in the tubules, especially in the loops of Henle. These changes, together with albuminuria, characterize a nephrosis which occurs likewise in rice-fed rabbits without beriberi. Somewhat similar, but often more intensive, degenerative changes were observed by Kozawa and Yamamoto (1924) in the renal convoluted tubules of rice-fed rabbits.

Riquier (1925) found renal parenchymal changes in rice-fed pigeons, especially in the terminal stages. The changes included cloudy swelling, congestion and, rarely, small hemorrhages, but never the severer lesions described by some authors. Wake and Suzuki (1925), on the other hand, found a nephrosic, contracted kidney in seven of over 100 white rats on Hofmeister's diet deficient in vitamin B (polished rice and canned meat). Marked atrophic and degenerative changes, hyaline cylinders and allied signs appeared in the tubular epithelium, with slighter changes in the glomeruli. The interstitial connective tissue showed increase with round cell infiltration.

In Kepler's (1925) case of beriberi in an adult, the urine showed a slight amount of albumin with many casts, leukocytes and red cells, indicating renal involvement. Both cortical and medullary hemorrhages were noted in the kidney at necropsy by Moore and Brodie (1927) in their case of infantile beriberi. In beriberi in adults, Bernard, Bablet and Guillerm (1927) observed the renal condition as a toxic parenchymatous nephritis, not truly inflammatory in character. The changes

involved a progressive epithelial degeneration and necrosis, with congestion, and sometimes edema, intertubular hemorrhages or interstitial sclerosis. The kidneys at necropsy grossly appeared normal. Somewhat similar renal lesions were produced in the pig by infection with *Bacillus asthenogenes*. Renal disturbances in beriberi in man were noted also by Scott and Herrmann (1928).

Reproductive Tract: Dietary deficiency of vitamin B results in marked atrophy of the gonads (testis or ovary). This observation was made by Ogata and his associates, Lopez-Lomba and Randoin, Riquier and Simnitzky in pigeons and fowls, and by Murata in rabbits. The loss in the testes of pigeons may reach 90 per cent within from fifteen to twenty days (Simnitzky). This loss involves a progressive atrophy and degeneration of the seminiferous epithelium, which may finally be reduced to a single layer of supporting Sertoli cells (Murata). Murata (1923) found the interstitial tissue somewhat increased in rabbits, but Riquier (1925) was uncertain as to this change in pigeons. Ogata with others (1921) described an increase in the fatty granular content of the interstitial cells, which Simnitzky (1926) ascribed to an increased resorption of substances derived from the degenerated seminiferous epithelium.

The ovarian changes have been less extensively studied. In beriberi in rabbits, according to Murata, the atrophy involves the stroma, as well as the follicles, which are few and small. The interstitial cells are not apparent. Dulzetto (1927, 1927a) stated that the nuclei of the ovarian interstitial cells disappear, while the lipoidal granules become chemically changed so as to stain with hematoxylin instead of sudan III. However, germinal atrophy of the ovaries and the testes is not specific for the deficiency of vitamin B; it may appear in various forms of malnutrition, as observed by Yamasaki (1923) and many others.

Parkes and Drummond (1925) found in rats a decrease in fertility that was associated with degeneration of the testis and was, in general, proportional to the degree of the deficiency of vitamin B. In extreme cases, the testis sometimes failed to regenerate, so that sterility persisted in spite of recuperation of the normal body weight and vigor on restoration of the missing vitamin to the diet. Marrian and Parkes (1928) found that the degeneration of the testis in pigeons deficient in vitamin B is not necessarily a starvation effect, but is probably caused by lack of the antineuritic factor. Mattill (1927) and Evans (1928a) concluded that in the rat the degeneration of the testis hitherto ascribed to a deficiency of vitamin B is in reality due to an associated deficiency of vitamin E, and can usually be prevented by provision of the latter in the diet.

Suprarenal Gland: McCarrison's discovery of suprarenal hypertrophy in polyneuritic pigeons has received abundant confirmation, but

there is much confusion as to the details and significance of the associated changes. Bierry and his co-workers (1920) advanced the hypothesis (not confirmed by more recent work) that there is an associated hyperadrenalinemia which produces a generalized vascular sclerosis throughout the various organs. Hypertrophy of the suprarenal glands was noted in polyneuritic pigeons by Lopez-Lomba and Randoin (1923) and McCarrison and Norris (1924). Ogata and his associates (1920, 1921, 1924a) found in pigeons a suprarenal hypertrophy of only 17 per cent during the period of incubation (about the same as in starvation), and an increase to 79 per cent during the period of acute symptoms. In chickens the hypertrophy was smaller (from 25 to 56 per cent). Histologically, the suprarenal cortex showed marked hypertrophy with numerous mitoses, but not degenerative changes. The cholesterol esters decreased; other fats were unchanged. There was little, if any, change in the medulla; or in the chromaffin reaction. Beriberi in man differs, they claimed (1924), in that the hypertrophy occurs in the suprarenal medulla. According to von Beznak (1923), the twofold or threefold enlargement of the suprarenal glands in beriberi is not due to simple inanition, since it does not occur in pigeons fed yeast only. The epinephrine content is decreased rather than increased. Riquier (1925) described the cortical changes in great detail. In advanced stages, there occurred marked vascular congestion, hypertrophy and hyperplasia of the cell-cords and reduction of fats. The medulla did not show any change except at death; then the cells appeared vacuolated and the nuclei pyknotic, while the chromaffin reaction was decreased or absent. Lasowsky and Simnitzky (1926), in pigeons, found the hypertrophy of the suprarenal glands proportional to the length of the period of deficient feeding. The hypertrophy was greater in the cortex than in the medulla. There was a progressive infiltration of fat in the cortical cells, due to hyperlipemia, with an associated hypertrophy and hyperplasia of the cells. The cells of the medulla also became hypertrophied, with nuclear enlargement and a decrease in chromaffin granulation. Kon and Drummond (1927) concluded that there is probably a hypertrophy of the suprarenal glands, but not any change in the content of epinephrine.

In beriberi in rabbits, according to Murata (1923), the increase of 35 per cent in the weight of the suprarenal glands is caused by cortical enlargement. There is hypertrophy, and probably hyperplasia, of the cells of the zona fasciculata. These cells usually show a marked increase in lipoid content, an increase probably due to hypercholesteremia. Verzár and Péter (1924) found the weight of the suprarenal glands increased 70 per cent in rats and 100 per cent in rabbits. The increase was apparently due to cortical hypertrophy. Wax model reconstructions indicated an increase of about 50 per cent in the ratio of the cortex

to the medulla. They suggested that this cortical enlargement may have been a compensatory hypertrophy, in connection with a disturbance of the cholesterol metabolism. Drummond and Marian (1926) noted that in rats either starved or on a diet deficient in vitamin B the suprarenal hypertrophy was associated with hyperglycemia. Woollard (1927), however, did not discover histologic changes in the cortex or the medulla in Drummond's test rats. Kolliner (1927) noted variable changes in the ratio of the nucleus to the plasma of the suprarenal cells in rats on diets variously deficient. According to Marrian (1928) the suprarenal hypertrophy in pigeons deficient in vitamin B is caused chiefly by lack of the antineuritic (B_1) factor, although B_2 is contributory.

Thyroid Gland, Parathyroid Glands and Hypophysis: In polyneuritic pigeons, Ogata and his associates (1920, 1921) noted, in general, a decrease in the weight of the thyroid gland, but did not observe hyperemia, or any abnormal structure. Lopez-Lomba and Randoin (1923) reported a decrease of 28 per cent in the weight of the thyroid gland in polyneuritic pigeons. Riquier (1925) found in the thyroid gland a constant hyperemia with occasional hemorrhages, especially in pigeons that had died of beriberi. Desquamation of the follicular epithelium sometimes occurred, but marked changes in the colloid or the interstitial connective tissue did not appear.

In beriberi in rabbits, Murata (1923) observed a marked decrease in the weight of the thyroid gland, with, apparently, a follicular atrophy. Nicholson (1924) described a fragmentation and reduction in the number of mitochondria in the thyroid cells of rabbits and guinea-pigs under various conditions, including a deficiency of vitamin B. McCarrison (1927) reported an increase of from 50 to 100 per cent in the weight of the thyroid gland in rats on a defective diet, in which a deficiency of vitamin B was probably the chief factor. The goiter presented signs of hyperactivity, with later an exhaustion of the epithelium, which was replaced by nonsecretory cells and fibrous tissue. Somewhat similar results were obtained by Satwornitzkaja and Simnitzky (1927) in rats and pigeons.

Fukushi (1924) studied the thyroid gland in twenty-eight cases of beriberi in adults and in six cases in infants. The weight of the thyroid gland was usually above normal, although the size appeared subnormal in the adults. The follicles were decreased in size. In the adults, the epithelium was cubical or flattened (atrophic), desquamation frequent, necrosis rare, epithelial lipoids and pigment abundant, hemorrhages somewhat frequent and colloid thin. In the children, the epithelium was cubical, proliferation frequent, lipoid scarce, pigment absent, colloid thin and interstitial connective tissue somewhat increased.

In polyneuritic pigeons, Ogata (1920) noted a decrease in the size of the parathyroid glands, with some cellular changes. Riquier (1925),

however, found the parathyroid glands normal. Tanabe and Yoshimura (1920) gave measurements on the size of the parathyroid gland in thirty cases in man, but his conclusions were uncertain in the absence of norms for comparison. The parathyroid glands presented a parenchymatous hypertrophy, with little adipose tissue. The light chief cells appeared to be increased in relative frequency.

Ogata (1920) did not observe in rice-fed fowls and pigeons any definite change in the weight or structure of the hypophysis; but with his associates he later (1921) found an increase in weight with colloid occurring in the cell-cords of the hypophysis. This was confirmed by Riquier (1925), who observed also congestion with frequent mitoses and an increased lipoid content in the chromophil cells. Murata (1923) found in beriberi in rabbits an apparent slight loss of the weight of the hypophysis. Satwornitzkaja and Simnitzky (1928) noted increased vacuolation, especially of the basophil cells, which was more pronounced in pigeons than in rats.

Thymus and Spleen: Marked atrophy of the thymus in rice-fed pigeons was observed by Ogata and his associates (1920, 1921), Lopez-Lomba and Randoin (1923) and Riquier (1925). In beriberi in rabbits, Murata (1923) likewise noted this extreme thymic atrophy, even with relatively slight loss in body weight. The thymic lymphocytes underwent retrogression and Hassall's corpuscles became rare.

Marked atrophy of the spleen in rice-fed pigeons was found by Ogata (1920), Lopez-Lomba and Randoin (1923) and Riquier (1925); and in beriberi in rabbits by Murata (1923). This atrophy (like that of the thymus) apparently occurred irrespective of loss in the weight of the body. Atrophy was observed in the red pulp as well as in the white pulp, and hemosiderin deposits were increased in the reticulo-endothelial cells. Riquier also noted a decrease in size with follicular atrophy of the lymphatic glands in various regions (pigeons). The bone marrow showed enlargement of the adipose cells, but a decrease in the hemoblastic elements (myelocytes, erythroblasts and megakaryocytes).

Blood: In general, the atrophy of the hematopoietic tissues tends to cause anemia during inanition from a deficiency of vitamin B, but the results appear variable. Ogata (1920) observed in chicks on a diet of rice (with forced feeding) a preliminary increase in the erythrocyte count, with a decrease later. The leukocyte count (polymorphonuclears) tended to increase, although the lymphocyte count remained unchanged. Ogata and his associates (1924) held that a decreased number of both erythrocytes and lymphocytes is one feature distinguishing B-avitaminosis of animals from beriberi in man. Riquier (1925) in polyneuritic pigeons found a progressive decrease in the erythrocyte count (from 4,500,000 to 2,500,000). The leukocyte count (pseudo-eosinophils) and

the number of platelets increased, and then decreased in the final period. Morphologic changes in the red cells (poikilocytosis and like conditions) were also noted by Riquier and Ogata. Barlow and Biskind (1928) found a decrease in red cell count, associated with relative hydremia, Suzuki (1924) also reported anemia and lymphopenia in test pigeons. De Gasperi (1926), on the other hand, did not find any significant change in the erythrocyte count; but found an increase in the percentage of polymorphonuclear neutrophils and in that of basophils, with a corresponding relative decrease in the percentage of lymphocytes. Little change in the fat and lipoid content of the blood was found by Tawamura (1924) in beriberi in chickens, and by Iwatsuru (1925) in rabbits. In beriberi in rabbits, anemia was observed by Murata (1923) and Verzár and Kokas (1924), which accords with the marked atrophy of the hematopoietic tissue noted by Ozawa (1922) and Murata (1923). The adipose bone marrow underwent a gelatinous metamorphosis, as in starvation. Sherif and Baum (1927) concluded that a deficiency of vitamin B did not have any definite effect on the thrombocyte or erythrocyte count in rats.

Skeleton: In addition to the aforementioned atrophy of the bone marrow, osteoporosis, with a tendency to spontaneous fractures, was found in beriberi in rabbits by Ozawa (1922) and Murata (1923). Also, hemorrhages in the bone marrow were noted occasionally by Ozawa (1922) in rabbits and by Sure (1927, 1927a) in young rats. Sure and Schilling (1928) found these hemorrhages conspicuous and nearly constant.

Effects of Deficiency of Vitamin C (Antiscorbutic).—Epidemic scurvy has been one of the scourges during both remote and recent years of war and famine, especially in Russia. Tschernorutzki (1922) reported observations on 4,227 cases in adults. According to Schagan (1924), the highest incidence was in children. In the St. Petersburg Children's Clinic, cases of scurvy were rare before the war, but formed 11.3 per cent of all cases in 1920. Beeuwkes (1926) reported that in certain Russian districts in 1921 over 75 per cent of the population had scurvy, with a mortality reaching 50 per cent of the hospitalized cases. "Hunger edema" (in which, as has been mentioned, a deficiency of protein is probably the chief factor) was a frequent complication, according to the literature reviewed by Herzenberg (1926). Shipley and Chavarria (1924) noted a great increase in infantile scurvy after the pasteurization law became effective in Baltimore, in 1917.

Kompanejetz (1923) observed that rhinitis sicca anterior was often present in scorbutic Russian soldiers. The septal wall appeared scabby and there was an associated epistaxis in about one third of all the cases. The literature cited by Place (1925) indicates that exophthalmos, pro-

duced by orbital hemorrhages, appears in about 10 per cent of all cases of infantile scurvy. Bullowa (1927) described a case of mixed scurvy and beriberi in a hotel porter who had lived for four and a half months on tea and bread. Abels (1924) maintained that "dysergy," or predisposition to infection, is a characteristic feature in scurvy, and that many of the usual symptoms (including the hemorrhages) are chiefly secondary to the associated infections.

The variation in susceptibility to scurvy according to the species is well known. Beard (1926) found that for normal growth in the mouse (as in the rat), vitamin C is apparently not a dietary essential. Thurston, Eckles and Palmer (1926) reached a similar conclusion for the calf. Goss (1925) and Meyer and McCormick (1928, 1928a) gave detailed accounts of the lesions in scorbutic guinea-pigs. Anderson and Smith (1924) concluded that the loss in weight in guinea-pigs during scurvy cannot be attributed to simple inanition alone.

L. F. Meyer (1923) recognized three stages in human scurvy: (1) a latent stage (which may continue indefinitely), characterized by a tendency to hemorrhages, owing to abnormal permeability of the vascular walls, especially in the skin and mucosae; (2) appearance of gingival hemorrhages and pains in the long bones and costochondral joints, and (3) development of the typical scorbutic symptoms, with involvement of the supporting tissues, widespread hemorrhages and other conditions. Andresen (1923) described (1) a latent scorbutic stage, with pains along the nerve trunks and cutaneous cyanosis; (2) a stage of active scurvy, with typical hemorrhages and other characteristic conditions, and (3) a stage of retrogression, with resorption of the hemorrhagic exudates, scleroderma, etc. Tschernorutzki (1922) gave detailed statistics on the occurrence of the various symptoms in scurvy in adult human beings. Friderichsen (1927) emphasized the variation in localization of early scorbutic symptoms in children according to age. In infants, the dominating symptoms appear, he stated, in the long bones. In older children, the muscular system is affected more, "growing pains" being a frequent prescorbutic myopathy. In older persons, extensive hemorrhages in the skin occur. Shattuck (1928) concluded that well marked scurvy in the adult may easily pass unrecognized.

Mouriquand and his associates (1924) found that although adult guinea-pigs might recover fully on an antiscorbutic diet, about 65 per cent of the younger animals failed to recuperate and passed into a chronic condition resembling athrepsia in man. Even those apparently fully recovered appeared more susceptible to a second attack of scurvy. This was at first ascribed to persistent lesions in the bone marrow, but later (1924a) to lesions in the liver. Fujihira (1923), however, did not find an increased susceptibility to a second attack of scurvy in guinea-pigs.

Smith (1927) found that guinea-pigs on a basal scorbutic ration died in from ten to thirty days with acute scurvy. Those receiving, in addition, an insufficient dose of orange juice (0.5 cc. daily) usually lived from six to eight months in a debilitated state somewhat resembling infantile scurvy, with loss of weight, paralysis of the limbs, and other typical conditions. Gerstenberger and his associates (1924) noted that the symptoms of scurvy appeared to be less severe in pregnant guinea-pigs. Fetal scurvy in guinea-pigs was observed by Meyer and McCormick (1928, 1928a).

Wolbach and Howe (1925, 1925b, 1926) concluded from experiments on guinea-pigs that the scorbutic state affects primarily the supporting tissues, in which the cells are unable to produce and maintain the normal intercellular substances and structures. The hemorrhagic tendency is increased by the lack of intercellular cement in the endothelium, as held by Aschoff and Koch. Proliferative capacity is not lost by the endothelium, fibroblasts or osteoblasts. Meyer (1926) and Meyer and McCormick (1928, 1928a) found in scorbutic guinea-pigs a visceral fatty degeneration. This appeared to be secondary to a generalized autolysis, resulting in an extensive destruction of both the voluntary and the involuntary musculature, nervous system, skeleton, lungs and abdominal viscera. Meyer held that this widespread cellular degeneration, rather than defects in the cement substance or supporting tissues, is the fundamental lesion in scurvy. Stettner (1925) contributed a critical review of the literature on the etiology and pathology of scurvy and rickets.

Brouwer (1927) noted granular hematogenous pigment in various organs (spleen, suprarenal, alimentary canal, liver) of scorbutic guinea-pigs. Of the weights of the various organs, that of the eyeball and that of the kidneys remained nearly stationary; that of the suprarenal glands increased; that of the thymus (and to some extent the weights also of the heart, the pancreas, the thyroid and, probably, the ovary and the liver) decreased; while that of the spleen was highly variable.

Blood Vessels and Blood: Meyer (1926) and Meyer and McCormick (1928, 1928a) observed that the blood vascular endothelium in scorbutic guinea-pigs becomes swollen and detached, and that the vascular walls are deficient. The conclusions of Wolbach and Howe concerning endothelial cement have been mentioned. Bencini (1926) noted an abnormal extravasation of fluid on the intravenous injection of physiologic sodium chloride solution into the vessels of scorbutic guinea-pigs, resulting in perivascular edema around the great vessels in the abdomen, the neck and the hind limbs. Stefko (1927a) described in detail the degenerative changes in the walls of the intestinal blood vessels in scorbutic (?) victims of famine, with hemorrhagic diathesis. Novodvorskiy (1928) also described the blood vascular changes in scurvy in man.

Anemia, according to Aron (1922), is an early symptom in infantile scurvy. Schagan (1024) found the blood picture variable, with the erythrocyte count ranging from 3,000,000 to 4,500,000; the leukocyte count from 4,000 to 6,000 (of which the polymorphonuclear neutrophils made up 60.5 per cent, the lymphocytes 34.5 per cent, the eosinophils 1.5 per cent, the basophils 1 per cent and the monocytes 2.5 per cent). The leukopenia usually disappeared during convalescence. Ossinowski (1924) noted hypolymphocytosis (lymphopenia) in scorbutic Russian children. Shipley and Chavarria observed the erythrocyte count dropping as low as 2,480,000; and the leukocyte count varying from 5,000 to 15,000, even in apparently uncomplicated cases. The differential counts are also given. The effects of infectious complications are described. A relative lymphocytosis with a decreased number of neutrophils was observed by Tschernorutzki (1922) and Andresen (1923) in scorbutic Russian adults. Oppel and his co-workers noted anemia with thrombopenia and leukopenia in their study of scurvy in rabbits and in man. In infantile scurvy, Carbonara (1928) observed moderate anemia, poikilocytosis and anisocytosis, with marked decrease in hemoglobin content. In experimental scurvy, the changes in the blood were slight.

In scurvy in rabbits, Findlay (1923) and Bencini (1926) noted leukopenia. In guinea-pigs, Lesné and his associates (1923) found the red and the white cell count variable according to the stage of scurvy. Liotta (1923) noted a progressive anemia with slight leukocytosis, the differential count showing mononucleosis, neutropenia and eosinophilia. Verzár and Kokas (1924) did not find any change in either the white or the red cell count. Sherif and Baum (1927) likewise failed to observe any change in red cells or thrombocytes. Trentini (1927) noted an increase in the number and the size of the fat droplets in the monocytes of scorbutic guinea-pigs. Meyer and McCormick (1928, 1928a) found a decreased number of erythrocytes and a decreased number of lymphocytes, but an increased count of polymorphonuclears.

Gottschalk (1923) ascribed the anemia of infantile scurvy to a primary lesion of the bone marrow. In the bone marrow of scorbutic guinea-pigs, Findlay (1923) observed a gelatinous degeneration, and Mouriquand, Michel and Bernheim (1924) noted fibrosis with a greatly decreased number of lymphoid cells.

Skeleton: In addition to the aforementioned changes in the bone marrow, the effects of scurvy on the skeleton in guinea-pigs will now be considered. Shinya (1922) found that transplantation of metatarsal bones or phalanges from scorbutic into healthy guinea-pigs succeeded in one third of the cases, but the converse experiment failed. In guinea-pigs on scorbutic diet, according to Watanabe (1924) and Schilowzew (1928), fractured bones are not repaired, and the resorption

of traumatic exudates of blood is greatly retarded. On the other hand, underfeeding alone does not prevent new formation of bone. Murata (1924) concluded that the essential skeletal lesion in experimental scurvy is a degeneration of the periosteum and endosteum, causing an inability to ossify. Merely connective tissue cells are formed, which, as a granulation tissue, tend rather to resorption of bone.

Wolbach and Howe (1925b, 1926) found that during scurvy the formation of bone ceases immediately, although in places osteoblasts (and fibroblasts in general) continue to proliferate. These can form an ossified matrix within forty-eight hours, if antiscorbutic substances are fed. During scurvy, incisions in the bone are not repaired. Israel and Fraenkel (1926) observed marked retardation of the formation of the callus and of the healing process in fractures of the femur in scorbutic guinea-pigs.

Höjer and Westin (1924, 1925) and Westin (1925, 1925a) described the changes in the jaw bones as well as the teeth of scorbutic guinea-pigs. Meyer and McCormick (1928) observed proliferative changes in the costal cartilages and the bone marrow, with marked degeneration and disintegration of the walls of the blood vessels. According to Ossinowski (1924), in scurvy in man the skeleton is involved more frequently and more severely in children than in adults.

Noteworthy advances have recently been made in the roentgenology of the scorbutic skeleton. The excellent work of Wimberger (1923, 1924, 1925), when compared with that of Tobler (1918) from the same institution (Pirquet's pediatric clinic in Vienna), reveals striking progress both in the technic of making the plates and in the skill of interpretation. Wimberger emphasized the diagnostic importance of Fraenkel's "white line" (the "Trümmerfeldschatten"), which was questioned by Tobler and some other workers. It is admitted, however, that a somewhat similar shadow may appear in the zone of new calcification in healing rickets, and puzzling pictures may occur also in cases of intermittent or healed scurvy, as well as in the (not infrequent) mixture of rickets and scurvy.

Two other interesting features in the roentgenography of scurvy were presented by Wimberger. The first is the clear zone of rarefaction, corresponding to the trabecular resorption in the "Gerüstmark" (fibrous marrow) area of the diaphysis, adjacent to the denser "Trümmerfeld" zone. This rarefaction occurs likewise in the epiphyses, which become light, except in a denser peripheral border or ring (corresponding to a "Trümmerfeld"). The light epiphyseal centers had been observed previously by Reyher (1911) and Gött (1918), who did not recognize their diagnostic importance. Gött claimed that they appear not only in scurvy, but in various other atrophic conditions of the skeleton. Wimberger held that they are characteristic of scurvy,

and may persist in the epiphyses even years after clinical recovery. The occurrence and diagnostic importance of Wimberger's ring was confirmed by Pelkan (1925), Schwartz (1927) and Bromer (1928). Nassa (1925) held that the ring occurs only in cases of combined scurvy and rickets.

The second feature of interest is the appearance of from two to four, or more, cross-lines (near the end of the diaphysis), which represent former "Trümmerfeld" zones persisting from healed intermittent scurvy. These lines were previously noted by Tobler (1918) and especially by Frank (1920). Stettner (1925) and Harris (1926, 1928) think they represent cessations of osseous growth, which may occur normally during adolescence as well as following rickets or any form of acute illness or starvation. Bromer (1928) gave a thorough review of the literature together with data from fifty-six original cases illustrating the points in the roentgenologic diagnosis of scurvy.

Teeth: Williams (1923) reported profound degenerative changes in both the enamel and the dentine of guinea-pigs subjected to vitamin deficiencies resulting in a condition related to scurvy. Wolbach and Howe (1925, 1925b, 1926) paid special attention to the teeth, in which the earliest effect of scurvy is found. The odontoblasts in the incisor teeth become separated from the dentine and undergo striking changes in size, arrangement and staining reaction. Normal structure may be reestablished within forty-eight hours after the feeding of antiscorbutic foods. Smith (1927) noted frequent fractures of the teeth in chronic scurvy of guinea-pigs; while Meyer and McCormick (1928, 1928a) found hemorrhages in the pulp of the incisors.

An especially thorough study of the changes in the teeth of scorbutic guinea-pigs was made by Höjer and Westin (1924, 1925) and Westin (1925, 1925a, 1926). The principal lesions found were: (1) the gradual change and disappearance of the odontoblastic layer; (2) the amorphous calcification of the predentin and the absence of Tomes' canals in this layer; (3) the old dentin's becoming porous; (4) the new formation of pulp bone instead of dentin; (5) hyperemia and sometimes hemorrhages, necroses and subsequent hydropic changes in the pulp and (6) later variable atrophy and resorption of the pulp bone, dentin and pulp tissue.

Alimentary Tract: Oral lesions, especially of the gums, are characteristic symptoms of scurvy in man. The gingival changes were described by Tschernorutzki (1922), Ossinowski (1924) and Scholle (1924). They occurred in 90 per cent of the Russian adults and in 100 per cent of the children. The stomatitis became gangrenous in 13 per cent of the cases, according to Schagan (1924), and in 15 per cent of Tschernorutzki's 4,227 cases. Mouriquand and his co-workers (1924)

did not find any significant lesions in the intestines of scorbutic guinea-pigs, although intestinal atrophy was noted in those which failed to recover when refed a normal diet. Carra (1925) described areas of variable degeneration in the mucosa and muscularis mucosae of the small intestine, and to a lesser extent in the stomach and large intestine, in scorbutic guinea-pigs; while Guarino (1927) found gastric congestion, hemorrhages and disappearance of the secretory granules in the gastric gland cells. Mucohemorrhagic diarrhea was described by Ossinowski (1924) as a grave symptom in infantile scurvy. According to Scholle (1924), the intestinal hemorrhages are produced by ulceration of the intestinal wall.

Liver: In the liver of scorbutic guinea-pigs, Murata (1922) found in 80 per cent of the cases grayish spots of variable size. On microscopic examination, these spots presented necrotic areas, which were interpreted as anemic infarcts due to thrombosis of branches of the portal vein. Lopez-Lomba and Randoin (1923a) observed an increase in the weight of the liver. Carra (1925) noted a fatty infiltration but not any degenerative changes in the hepatic glandular epithelium. Mouriquand and his associates (1924, 1925) found marked lesions in the liver of previously scorbutic guinea-pigs that had failed to recover fully and had passed into a chronic state of cachexia after being placed on a normal diet. In these cases, the liver appeared atrophic, with enormous capillary dilatation and multiple hemorrhages. The liver cells were atrophied, without fatty degeneration, and the nuclei were of normal size. Meyer and McCormick (1928, 1928a) noted fatty degeneration of the liver as one of the most conspicuous lesions in scorbutic guinea-pigs. Detached masses of liver cells were seen in the large hepatic veins.

Pancreas: Murata (1922) and Carra (1925) observed a slight hypertrophy and hyperplasia of the pancreatic islets of Langerhans in scorbutic guinea-pigs. Murata pointed out the probable significance of these changes in relation to the co-existent hyperglycemia. Fatty degeneration in the pancreas was noted by Meyer and McCormick (1928, 1928a). According to Löwy (1923), the pancreatic islets appeared strikingly larger and more numerous in scorbutic guinea-pigs; but changes were not found in starvation.

Spleen and Thymus: In scorbutic guinea-pigs, Lopez-Lomba and Randoin (1923a) found little, if any, change in the weight of the spleen, but Mouriquand and his associates (1924) observed splenic atrophy. Brouwer (1927) found the spleen variable in weight, with deposits of hematogenous pigment. Oppel and his fellow research workers (1924) suggested that the hemolytic action of the spleen is inhibited by a suprarenal hormone, which is decreased in scurvy.

A marked atrophy of the thymus was noted in scorbutic guinea-pigs by Morikawa (1920), Lopez-Lomba and Randoin (1923a) and Brouwer (1927).

Kidney: In scorbutic guinea-pigs, Murata (1922) observed occasionally what he termed "metastatic calcification" in the kidney, although Lopez-Lomba and Randoin (1923a) found little, if any, change in the weight of the kidney. Meyer (1926) and Meyer and McCormick (1928, 1928a) noted a marked fatty degeneration in the epithelium of the kidney and other organs. Mouriquand and his associates (1924) did not find any significant lesions in the kidneys of athreptic guinea-pigs that failed to recover after antiscorbutic feeding.

Reproductive System: A marked atrophy of the testis in scorbutic guinea-pigs was noted by Morikawa (1920); while Lopez-Lomba and Randoin (1923a) found only a slight loss of 12 per cent. Mouriquand, Michel and Sanyas (1923) observed an early effect on spermatogenesis, with almost complete destruction of the seminiferous epithelium in some places. Abnormal spermatic cells and spermatozoa were also observed. Medes (1926) and Lindsay and Medes (1924, 1926) found but little apparent change in the weight of the testis after ten days on a scorbutic diet. The blood vessels appeared congested, with degeneration of the seminiferous epithelium in some tubules. Multinucleated or giant cells, such as occur during starvation, were not found. Other tubules showed normal spermatogenesis. Guinea-pigs, previously scorbutic for from thirty to forty days, had almost completely recovered the normal structure of the germinal epithelium after seventeen days on an antiscorbutic diet. Disintegration of the seminiferous epithelium was noted by Meyer and McCormick (1928, 1928a).

Marked atrophy of the ovary in scorbutic guinea-pigs was also observed by Morikawa (1920), but observations of the structure were not recorded.

Endocrine Organs: A marked increase in the weight of the thyroid gland in scorbutic guinea-pigs was noted by Lopez-Lomba and Randoin (1923a). Brouwer (1927), however, found a decrease. Mouriquand, Michel and Sanyas (1923) observed a slight congestion, a tendency to sclerosis and, often, small follicles. Morelli and Gronchi (1927), on the other hand, did not find sclerosis, but often found signs of hyperplasia and hypersecretion, especially in the thyroid glands of guinea-pigs dying early with atypical symptoms. Löwy (1923) did not see any histologic changes in the thyroid gland. The cells of the parathyroid glands appeared small. Harris and Smith (1928) found the follicular thyroid cells increased in number and height, with the colloid vacuolated and decreased in amount. Changes were not noted in starvation.

Suprarenal Glands: The marked hypertrophy of the suprarenal glands in the scorbutic guinea-pig was confirmed by Lopez-Lomba and

Randoin (1923a), and Brouwer (1927). Morikawa (1920) ascribed this hypertrophy to the co-existent condition of simple inanition. Mouriquand, Michel and Sanyas (1923) found the suprarenal glands congested (sometimes enormously), especially in the medulla, more rarely in the zona fasciculata. The superficial part of this zone presented a variable degree of fatty infiltration. Lindsay and Medes (1926a) noted changes similar to those previously described by McCarrison, with a variable amount of hemorrhagic infiltration in the cortex and medulla.

Morelli and Gronchi (1927) in the earlier stages of scurvy in guinea-pigs found signs of increased activity of the suprarenal glands, as shown by a siderophil substance, fuchsinophil granules, lipoids and doubly refractive fats. In later periods, there was an increase of fuchsinophil granules and siderophil cells, but a diminution of lipoids and doubly refractive substances. Most important was the cortical hyperplasia, with numerous mitoses; also amitoses. Besides these progressive changes, there were also regressive phenomena, due to numerous hemorrhagic foci, with zones of cloudy swelling and nuclear degeneration (pyknosis, chromatolysis and other typical conditions). In the medulla, the chromaffin reaction decreased, up to complete disappearance. On refeeding a complete diet after the first appearance of scorbutic symptoms, some of the animals recovered promptly; others died after from twenty to fifty days, with hemorrhagic lesions and fatty degeneration of the suprarenal glands. Meyer and McCormick (1928, 1928a) also mentioned degenerative changes in the suprarenal epithelium.

According to Rowles (1925), the apparent increase in the weight of the hypophysis in the scorbutic guinea-pig is due to congestion in the pars anterior, as shown by volumetric analysis. The parenchyma actually decreases in volume, with karyorrhexis and karyolysis in the later stages. Meyer and McCormick (1928a) also found various hemorrhagic and degenerative lesions in the nervous system and skeletal muscle.

Effects of a Deficiency of Vitamin D (Antirachitic).—The recent literature on the etiology and pathogenesis of rickets was reviewed by Howland (1923), Stettner (1925) and Hess (1928). McCollum's demonstration of the antirachitic vitamin D as distinct from vitamin A was accepted by Bloch (1923) and by most of the recent workers in this field. Davis (1923), however, and some more recent workers still supported the theory that vitamin A is the antirachitic factor. Thus, Zilva and his associates (1924) concluded that in pigs experimental rickets was produced when the amount of vitamin A present in the diet was sufficient to support growth but insufficient for ossification. According to Bohstedt and his associates

(1926) the "stiffness," or rickets, in swine is a disorder involving a deficiency of calcium, as well as of vitamins A and D. Marfan (1925) and Debray (1925) maintained that rickets in man is essentially a chondromyelitis (due chiefly to infections or toxins), and distinct from the experimental rickets in rats, which is essentially a chondroperiostitis.

Lobeck (1924) concluded that for production of rickets in rats, a deficiency of vitamin A is not essential (vitamin D was not recognized); that the proportions of calcium and phosphorus salts are of minor importance; and that absence of light is the effective agent. Lang (1925) held that both a dietary deficiency of vitamins and a lack of sunlight are the pathogenic factors. Various workers have recently demonstrated that vitamin D can be produced by ultraviolet radiation of a provitamin substance (ergosterol), either within the living body or in the food outside the body. This topic was reviewed by Hess (1928). Orgler (1927) concluded that rickets is essentially a disturbance of the intermediary calcium and phosphorus metabolism, which is normally regulated through (1) small amounts of vitamin D (arising from provitamin, activated by ultraviolet rays) and (2) endocrine secretions regulating salt metabolism. Von Bosányi (1925) emphasized the bone marrow as the seat of the antirachitic factor, since marrow extracts prevented or cured rickets. Holst (1927) still refused to accept the theory that rickets is caused by a deficiency of any vitamin; he believed that it is produced by some toxic substance present in cereal diets.

As to the frequency of rickets in man, Hess of New York held that it is the most common malnutritional disease, and that fully three fourths of the infants in the great cities are affected in some degree. Similarly, Blum and Mellion (1926) of New York reported that "fully 75 per cent of all artificially fed and perhaps 50 per cent of all breast fed infants manifest evidences of mild rickets at some time during the first two years of life." Beeuwkes (1926) found 80 per cent of the children with the disease in some districts of Russia. Schlesinger (1924) reported much smaller figures for German infants and small children, among whom the proportion of those that were rachitic reached a maximum of 25 per cent in 1918-1919, decreasing later to 15 per cent, but increasing again to 20 per cent in 1923.

Hess and Weinstock (1926) concluded that in the rat and in the human species rickets can be modified to some degree, but not entirely prevented, by the character of the maternal diet. Grant and Goettsch (1926), on the other hand, showed that young rats develop severe rickets when the mother's reserve of antirachitic vitamin is depleted by continuous reproduction in darkness and on diets deficient in this vitamin. Hess and his associates (1928) observed that vitamin D is essential for the embryonic development of both fish and chick.

The importance of age as a factor in predisposition to rickets was emphasized by Eckstein (1924) and Rabl (1925). Rabl found that in young rats (from 5 to 12 weeks old) a deficiency of light and of vitamin D usually caused rickets, while in older rats it produced merely osteoporosis. Abels (1927) stated that late rickets (adolescent osteopathy) occurs much more frequently in males than in females.

The variation in susceptibility according to the species appears in rickets as well as in other disorders due to dietary deficiencies. Beard (1926) could not produce rickets in mice. The rabbit also was generally found not susceptible to rickets, but Goldblatt and Moritz (1925) were successful with forced feeding of a diet deficient in phosphorus and the antirachitic factor but rich in calcium. Okamoto (1924) likewise produced rickets in young rabbits by a diet which causes scurvy in guinea-pigs. The effect of a deficiency of vitamin D in reducing the natural immunity against infections in various animals was shown by Mellanby (1926) and Eicholz and Kreitmaier (1928). Green and Mellanby (1928), however found that vitamin D does not prevent the pyogenic lesions due to deficiency in vitamin A.

Weight and Length of the Body: From observations on 870 rachitic infants, Wiltsche (1924) concluded that in the first half year, the growth in the length of the body is markedly retarded, even in mild cases. Both the trunk and the limbs are involved. The weight is correspondingly retarded, but the girth of the chest is above normal. In the second half year, the results are nearly the opposite, both stature and weight appearing above normal. Abdominal enlargement (present in 90 per cent of all cases) is due to gaseous distention of the intestines. Variot and Nazarie (1925, 1926) studied 233 rachitic children, of whom only fifteen were less than 6 months of age, the others being from 6 months to 2 years old. As to stature, the following percentages were found: 20.2 above normal; 44.3 normal and 35.5 below normal; as to weight: 31.3 above normal; 31.8 normal, and 36.9 below normal. Weight and stature ran parallel in 85 per cent of the cases, with dissociation in 15 per cent. Children surviving rickets are evidently, in most cases, able to recover later any deficiency in height or weight, according to the observations of Chase (1914) in Munich and of Wimberger (1925) in Vienna.

Teeth: Blum and Mellion (1926) reviewed the question concerning the diagnostic value of delayed dentition as a sign of rickets. They concluded that, although the dentition is usually delayed, even in mild rickets, this has little diagnostic significance since there is a normal variability in the time of the eruption of the deciduous teeth. Variot and Nazarie (1925, 1926) found that the eruption is retarded less frequently than is generally believed. Among thirty-seven atrophic rachitic infants, thirty-two had cut their teeth normally. Among

sixty-three hypertrophic rachitic infants, the dentition was normal in fifty-three. The relation of variously deficient diets to caries of the teeth was discussed by Mellanby, Pattison and Proud (1924). By feeding experiments on institutional children, it was shown that dental caries is less marked in those on diets short of cereals but rich in calcium and calcifying vitamin.

Skeleton: According to Moore (1924), the first skeletal signs of infantile rickets are craniotabes (most easily determined at the mastoid fontanel), deformities of the chest and costomalacia or softening of the sternal ends of the ribs. Both genu valgum and genu varum are always preceded by abnormal lateral motility of the knee joint, which is often the first sign of rickets in the leg. From a study of 870 infantile cases, Wiltsche (1924) concluded that, simultaneously with the craniotabes, a slight "rosary" appears on the fourth, fifth and sixth ribs. The epiphyses of the limbs are involved somewhat later, the upper usually earlier than the lower (this observation confirmed Stoelzner's, and was opposed to Guérin's observations).

Abels and Karplus (1927) regarded the presence of craniotabes or an enlarged fontanel at birth as a prerachitic symptom. In some cases, as shown by Koeppe (1926) and Bohe (1928), there may be a rachitic distention of the ventricles of the brain without any external enlargement of the cranium. This condition, which can be diagnosed by the roentgen ray, is designated by Koeppe as hydrocephalus occultus.

Huldschinsky (1928) concluded that the craniotabetic thinning of the cranium does not correspond to the ordinary skeletal softening in rickets. He interpreted it rather as osteoporotic thinning of the cranial wall, secondary to the increased growth of the brain in rickets. Craniotabes responds to antirachitic therapy much less readily than do the ordinary skeletal lesions.

The interpretation of roentgenograms in connection with rickets (as also in connection with scurvy) has received much attention in recent years. The subject was discussed at length by Weech and Smith (1923), Lesné, Mahar and Colaneri (1924), Wilson (1926) and Wimberger (1923, 1925), whose contributions are especially noteworthy. Groover, Christie and Merritt (1925) also made an extensive and valuable study of 926 cases. A clinical diagnosis of rickets was made in 68.7 per cent of the cases, an x-ray diagnosis in 66.5 per cent. In the incipient cases, the x-ray diagnosis is apparently far more accurate than the clinical diagnosis. Hamburger and Siegl (1928) noted the deceptive appearance of a "pneumothorax rachiticus," caused by the thoracic deformity.

From the work of Haffa (1924) and of Breus and Kolisko, it is apparent that the deformities of the adult pelvic skeleton (which are of especial importance in relation to child-birth) often appear during

rickets in childhood. The pelvic deformity is usually, but not always, proportional to the severity of the rickets in general. Reyher (1922) and Koehler (1924) concluded that the calcification of the bony epiphyseal nuclei of rachitic children is in general not appreciably delayed. Plaut (1924, 1924a) held that during mild infantile rickets the centers of ossification appear without delay, as shown by the x-rays. In moderate or severe cases, the centers of ossification fail to become visible by x-rays; but in reality the centers are laid down in uncalcified form at the normal time, as shown by the extreme rapidity with which large centers later become visible through calcification when the healing process begins (as was noted by Fraenkel and Lorey). Only in the severest cases of rickets is there a true retardation in the centers of ossification. Lewin (1927) found the appearance of an epiphysis within an epiphysis at the lower end of the femur and the upper end of the tibia in a child who had apparently suffered from intermittent rickets. As mentioned before, in the discussion of scurvy, difficulty is sometimes encountered in differential diagnosis between scurvy and rickets by the roentgenologic method, especially in cases of intermittent or coincident scurvy and rickets.

Lobeck (1924) described in detail the histologic changes in the skeleton in rats with experimental rickets, which he considered equivalent to rickets in man. Marfan (1925) and Debray (1925), however, contended that while the lesions of the bones are somewhat similar, the osteoid tissue is formed in the rat chiefly from the periosteum (perichondrium), while in rickets in man it is formed largely from marrow elements. Thus (as has been mentioned), rickets in rats is considered by them as essentially a chondroperiostitis; rickets in man as a chondromyelitis. Dalyell and Mackay (1923) demonstrated that histologic evidence of rickets may appear in infants without any clinical or roentgenographic symptoms of the disease. Brockman (1927) described certain skeletal peculiarities found in "renal rickets," associated with chronic interstitial nephritis in children. These peculiarities are ascribed to the toxic condition resulting from renal insufficiency.

Neubauer (1925) demonstrated that in rachitic rats the skull becomes relatively shorter, that is, brachycephalic. From a study of the limb bones of rachitic pigs and calves, McGowan (1924) concluded that the structure in the affected epiphyseal regions is modified to a considerable extent by the abnormal mobility of these parts. Bohstedt and his associates (1926) found that the stiffness, or posterior paralysis, in rachitic pigs is caused by fractured vertebrae, which project into the vertebral canal and compress the spinal cord. "Beading" of the ribs is usually present, although the histologic structure often differs from that in typical rickets or osteoporosis. Nonidez (1926) described the skeletal lesions in avian rickets.

Bone Marrow: The importance of the lesions of the bone marrow in rickets in man was emphasized by Marfan (1925) and Debray (1925), as has been mentioned. According to Debray, the medullary lesions were discovered by Cornil and Ranvier, and have since been studied in detail by Marfan and others. The changes, which DeBray held occur in rickets in man, but not in experimental rickets in animals, include a proliferation of marrow cells, normoblasts and eosinophils; a degeneration of neutrophil myelocytes; the presence of megakaryocytes, myeloplaxes and small mononuclears, and the appearance of marrow cells around vessels and even under the periosteum. The capillaries appear congested, sometimes with small hemorrhages. In late stages, there is a proliferation of the fixed elements with variable fibrosis. These lesions in the marrow are correlated with changes in the blood, as shown by DeVilla and Cartia (1925) through smears of marrow from the tibia (Caronia's method). The marrow cell counts in twenty-two rachitic children indicated in general an increased myelopoiesis and erythropoiesis, with a larger percentage of myeloblasts, hemocytoblasts and immature red cells. The observations on the blood recorded by Maurer and his associates (to be mentioned later) also indicate the involvement of the bone marrow in rachitic rats.

Blood: The results of examination of the blood in rickets continue to be variable, like those of earlier observers. Kaneko (1924) in forty rachitic infants found a slight decrease in the average number of erythrocytes and of polymorphonuclear leukocytes; an increase in the number of small lymphocytes and the other counts normal. In 870 cases, Wiltsche (1924) found constant anemia of a variable degree in severe rickets; often also in light cases. Merlini (1926) reported in detail the condition of the blood in thirty rachitic infants, together with an extensive review of the literature. DeVilla and Cartia (1925), in general agreement with previous investigators of the blood in infantile rickets, found a slightly decreased red cell count, the leukocyte count variable (normal or showing variable leukocytosis or sometimes leukopenia), lymphocytosis constant (allowance being made, however, for the normal lymphocytosis of infants), the number of eosinophils usually normal or below, immature granulocytes frequent and sometimes nucleated reds. The observations were correlated with those on smears from the bone marrow, as has been mentioned. Stransky and Wittenberg (1926) concluded that infantile anemia is due to hypofunction of the bone marrow, with a decreased number of red and white cells and platelets. When anemia occurs during rickets, the examination of the blood helps to indicate the stage and the severity of the rickets, and the blood improves parallel with the general recovery on antirachitic treatment. Baumann (1928) ascribed the anemia to lack of iron.

In rachitic rats, Maurer and his associates (1925) found but little change in either the total or the differential leukocyte count. But the constant appearance of erythroblasts in the blood after from three to five weeks and of myelocytes after seven weeks indicates the involvement of the bone marrow. Sherif and Baum (1927) did not find any significant changes in the hemoglobin content or the erythrocyte count of rachitic rats. They observed, however, a marked thrombopenia, which occurred likewise during a dietary deficiency of vitamin A, but not during a deficiency of vitamins B and C.

Spleen and Lymph Nodes: In rachitic puppies, Davies (1923) noted hyperplasia of the lymphoid tissue in the spleen and the lymph nodes. Giant cells were fairly numerous. Wiltsche (1924) found splenic enlargement in all anemic rachitic infants (29 per cent of 870 rachitic infants). The lymph nodes (inguinal, axillary and cervical) were enlarged in about the same percentage of cases, but Wiltsche ascribed this enlargement to causes other than the rickets.

Gonads and Endocrine Organs: In young rats with rickets (complicated by a deficiency of vitamin A), Eckstein (1923) found a marked atrophy of the testis and degeneration of the seminiferous tubules with a failure of spermatogenesis. The ovaries were more resistant and appeared normal in structure, although conception did not occur.

According to Davis (1923), the most striking change in rachitic puppies, aside from the lesions of the bones, was in the thyroid gland. The follicles were enlarged and filled with colloid. It has long been known that enlargement of the parathyroids occurs in rachitic rats (Erdheim) and in infants (Ritter). A similar parathyroid hypertrophy in rachitic chickens was recently observed by Doyle (1925) and Nonidez and Goodale (1927). The latter authors found that the enlargement involved both hypertrophy and hyperplasia of the parenchyma cells. Later there is a phase of regression, in which the epithelial cell cords appear shrunken, but this may coincide with hyperplasia of the stroma. In some cases, the parathyroid glands showed localized degenerative changes, mucoid or keratinous, of doubtful significance.

(To be Concluded)

Notes and News

University News, Promotions, Resignations and Appointments.—Claude H. Forkner and Leone McGregor have been granted fellowships for the study of pathology by the medical fellowship board of the National Research Council.

The following announcements effective July 1, have been made by the University of California Medical School: Isabel H. Perry has been appointed instructor in pathology; A. M. Moody, instructor in pathology, and S. R. Mettier, assistant professor of medicine and pathology (absent on leave 1929-1930). Z. E. Bolin was promoted from instructor in pathology to assistant professor of pathology, and J. F. Rhinehart from assistant in pathology to instructor in pathology.

Stuart Graves, dean and professor of pathology, University of Alabama School of Medicine, gave the Alpha Omega Alpha lecture at Augusta, June 1, on "Relationship between Premedical Education and Medical Education," and on June 3 addressed the graduating class on "American Medicine and Young Graduates."

Arthur T. Delaney has resigned his fellowship for work in pathology under the medical fellowship board of the National Research Council to accept the position of pathologist to the Englewood Hospital, Chicago.

William H. Welch has resigned as a member of the state board of health of Maryland after a continuous service of thirty-one years; Thomas S. Cullen succeeds Dr. Welch.

Germanus J. France, Baltimore, has been appointed automobile coroner according to a new law that provides for a separate coroner to investigate deaths caused by automobile accidents.

William D. Collier has been made director of the department of pathology and has been promoted to a full professorship at the St. Louis University School of Medicine.

George H. Whipple, professor of pathology in the University of Rochester, has been elected member of the National Academy of Sciences.

Theobald Smith has retired from the directorship of the department of animal pathology of the Rockefeller Institute for Medical Research, and Carl Ten Broeck is now acting director.

Nathan C. Foot, professor of pathology, University of Cincinnati College of Medicine, will spend a sabbatical year of study abroad, returning in the fall of 1930.

Leon H. Collins, Jr., who has been working in biochemistry and pathology under the medical fellowship board of the National Research Council, has accepted a position in the department of pharmacology in the University of Pennsylvania.

Eugene L. Opie, Philadelphia, has been awarded the Trudeau Medal of the National Tuberculosis Association for his work on tuberculosis in childhood.

Eugene C. Woodruff, who has been working in pathology at Vanderbilt University under the medical fellowship board of the National Research Council, has accepted a position in the department of pathology at Vanderbilt.

Mary Stevenson has been appointed assistant in pathology and Clyde W. Holland has taken the chair of bacteriology at Dalhousie University, Nova Scotia.

Society for Experimental Biology and Medicine.—The newly elected officers are: president, Peyton Rous; vice president, David Marine; secretary-treasurer, A. J. Goldforb; councillors, F. P. Gay and G. B. Wallace.

Federation of American Societies for Experimental Biology.—The meeting this year will be replaced by that of the Thirteenth International Physiological Congress in Boston, from Aug. 19 to 23, 1929. There will be no scientific

session of the societies of the federation as such, but the usual business meetings of the federated societies will be held on August 19, prior to the opening session of the congress.

Fellowships and Scholarships in the Medical Schools of the United States and Canada.—The second part of the *Journal of the Association of Medical Colleges,* vol. 4, no. 2, April, 1929, gives an authoritative list of fellowships and scholarships available in the medical schools of the United States and Canada.

Reduction in Price of Biography of T. Mitchell Prudden.—It will be of interest to pathologists to note that the price of "Biographical Sketches and Letters of T. Mitchell Prudden," pioneer American pathologist and professor of pathology in the College of Physicians and Surgeons, Columbia University, from 1892 to 1909 (pages 311, New Haven, Conn., The Yale Press), has been reduced to $2 a volume.

Endowment of Fellowships.—The Lucius N. Littauer Foundation has made a grant of $50,000 to Albany Medical College for three research fellowships, two in pathology and one in physiology and medicine.

International Congress of Microbiologists.—The meeting which was to be held at the Pasteur Institute in Paris in October, 1929, has been postponed until June, 1930. American microbiologists are invited to take part in the congress.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EFFECT OF BILE SALTS UPON UTERINE CONTRACTIONS AND UPON THE ACTION OF PITUITARY EXTRACT. J. HOFBAUER, Am. J. Obst. & Gynec. **16**: 245, 1928.

The effect of bile salts and their interaction with pituitary solution on the uterine muscle in the guinea-pig were studied. The experiments were made by kymographic readings of the contracting uterine horn in 50 cc. of Locke's solution. Diluted pituitary solution was added, and after its effect was demonstrated one-fourth strength sodium glycocolate was added. A suppression of the spontaneous uterine contractions followed, with a loss in muscle tone. It then took a much greater amount of pituitary solution to restore the uterine contractions and tone. In the pregnant uterus the bile salts had less effect and the muscle was more sensitive to the action of pituitary solution. This was most pronounced as full term was approached. The increase in the bile acid content of the blood during pregnancy has been demonstrated by others. This apparently holds the uterus in obeyance and tolerance to its increase in size. At term, when the uterus has become more sensitive, the suppressing power of bile salts is overcome by the hypophyseal secretions which have then become demonstrably increased.

A. J. KOBAK.

THE FEMALE SEX HORMONE. R. T. FRANK, M. D. GOLDBERGER and L. C. MCGEE, Am. J. Obst. & Gynec. **16**:387, 1928.

The vaginal spread test in the rodent is specific for the female sex hormone; and testicular extracts do not give a positive vaginal spread test when injected into castrated rats or mice.

A. J. KOBAK.

SUPRARENAL INSUFFICIENCY. L. C. WYMAN, Am. J. Physiol. **87**:29 and 42, 1928.

The lethal intraperitoneal dose of histamine acid phosphate for normal rats, and for those in which single suprarenalectomy had been performed was found to be over 100 mg. per hundred grams body weight. In animals in which double suprarenalectomy has been performed, it was diminished to about 7 mg. per hundred grams of body weight. This increased susceptibility persists unchanged for at least five months after operation. The presence of accesory cortical tissue, or of cortical transplants, did not affect this increase of susceptibility, while the presence of accessory chromaffin tissue appeared to afford protection. Complete or partial protection from fatal doses was also conveyed by the intraperitoneal injection of small doses of epinephrine hydrochloride. It is concluded that as the increase of susceptibility appears to be due to lack of medullary tissue, to the extent that it is valuable as a test of suprarenal function, it concerns that of the medullar rather than the cortex.

In rats, previous thyroidectomy was found not to affect the symptoms, the mortality rate, the susceptibility to diphtheria toxin and the susceptibility to histamine intoxication of suprarenalectomized animals. It was found that the intraperitoneal injection of from 6 to 10 cc. of 5 per cent dextrose solution may cause the death of suprarenalectomized animals, while such dosage is without effect on normal animals. In animals on which operation had been performed, smaller doses did not affect the increased susceptibility to histamine intoxication, and apparently not that to diphtheria toxin. In rats it would appear that dehydration is not an important factor in suprarenal insufficiency.

H. E. EGGERS.

THE UTILIZATION OF ACETOACETIC ACID BY NORMAL AND DIABETIC DOGS BEFORE AND AFTER EVISCERATION. I. L. CHAIKOFF and S. SOSKIN, Am. J. Physiol. **87**:58, 1928.

Sodium aceto-acetate injected intravenously into normal and eviscerated dogs disappears rapidly. Since there are not sufficient acetone bodies in the tissues several hours after the injection to account for the amount injected, it would appear that aceto-acetic acid can be utilized by muscle. In depancreatized dogs the aceto-acetic acid disappears more slowly, while in eviscerated diabetic dogs the disappearance takes place in the normal time. It is concluded that the excessive appearance of the acetone bodies in the tissue fluids of diabetic animals is not due to diminished utilization of them by the animal.

H. E. EGGERS.

THE RÔLE OF THE ANTERIOR PITUITARY IN HASTENING SEXUAL MATURITY IN RING DOVES. O. RIDDLE and F. FLEMION, Am. J. Physiol. **87**:110, 1928.

In a study of the effect on precocious sexual maturity in immature doves, it was found that daily anterior pituitary homeotransplants increased testicular growth, while a similar, but less marked, effect was obtained in some cases with ovarian growth. Similar effects were obtained by the intraperitoneal administration of a glycerin extract of fresh bovine anterior lobes. Body weight was not affected or was adversely affected. With the glycerin extracts, there was frequent enlargement of thyroids, livers and spleens.

H. E. EGGERS.

EFFECTS OF DIFFERENT FOOD SUBSTANCES UPON EMPTYING OF THE GALLBLADDER. W. F. KRAUSE and L. R. WHITAKER, Am. J. Physiol. **87**:172, 1928.

In cats, fats and fatty acids were by far the most active foods in emptying the gallbladder, the unsaturated fatty acids being apparently more active than the saturated. Pure carbohydrates had little or no effect, and proteins only a slight effect.

H. E. EGGERS.

MUSCLE HEMOGLOBIN CONCENTRATION DURING GROWTH AS INFLUENCED BY DIET FACTORS. G. H. WHIPPLE, A. H. GROTH and F. S. ROBSCHEIT-ROBBINS, Am. J. Physiol. **87**:185, 1928.

Litter-mated pups were fed on an adequate synthetic bread ration, or on a bread ration to which were added large amounts of cooked liver. After ten weeks' feeding there were no noteworthy differences in the concentration of muscle hemoglobin in the animals on the two diets. After from fifteen to twenty weeks on these diets, the pups which were fed liver showed a distinct increase both in blood hemoglobin and in the concentration of muscle hemoglobin. In contrast with the levels of blood hemoglobin, those of muscle hemoglobin are stable and are not easily disturbed. The maintenance factor required to replace the wear and tear of muscle hemoglobin is unknown.

H. E. EGGERS.

WATER RETENTION UNDER LOW BAROMETRIC PRESSURE. C. S. SMITH, Am. J. Physiol. **87**:200, 1928.

In dogs and rats kept under atmospheric pressures reduced from 2.6 to 9.8 cm. of mercury, water retention was observed. This retention was accompanied by restlessness, and it is suggested that this mechanism is concerned in the reaction by many animals and some human beings to approaching weather changes.

H. E. EGGERS.

COAGULATION TIME IN PARATHYROID TETANY. J. C. BROUGHER, Am. J. Physiol. **87**:221, 1928.

In parathyroidectomized dogs, there was a delay in blood clotting time during tetany varying from a few seconds to over thirty hours. The administration of

1 ounce (28.35 Gm.) of cod liver oil, or 0.4 cc. of acterol, restored clotting time to normal after a period of from two to four hours. If these were given for from twenty to forty days, the animals recovered, and their blood coagulation and serum calcium returned to normal.

H. E. EGGERS.

STUDIES IN THE DIGESTION OF LECITHIN BY PANCREATIC ENZYMES. SIDNEY A. PORTIS, J. A. M. A. **91**:1248, 1928.

Normal duodenal contents digest lecithin and gastric contents do not. In patients with cardiac decompensation there is a definite depression of enzyme activity as far as lecithin digestion is concerned. There is no apparent alteration in pancreatic enzyme activity in normal pregnant women. The pancreatic enzyme activity is depressed in the untreated duodenal ulcer and returns to nearly normal with the administration of alkalis. Patients with ulcers treated by the ordinary methods of rest in bed and food and without the administration of alkalis did not show a return to normal in the third week of management.

AUTHOR'S SUMMARY.

THE PHYSIOLOGICAL RESPONSE OF RABBITS TO INSULIN. M. SAHYUN and N. R. BLATHERWICK, J. Biol. Chem. **79**:443, 1928.

The rate at which sugar can be mobilized from the liver is an important factor in the determination of the responsiveness of an animal to the hypoglycemic action of intravenously injected insulin. Rabbits maintained on a diet rich in carbohydrates are markedly refractive. Rabbits whose reserve of sugar-yielding glycogen is, on the contrary, depleted, or cut off from mobilization as the result of splanchnectomy, are markedly responsive. More insulin is required to produce convolutions when given intravenously than when administered either subcutaneously or intraperitoneally.

ARTHUR LOCKE.

THE ENERY EXCHANGE IN OBESITY. J. M. STRANG and F. A. EVANS, J. Clin. Investigation **6**:277, 1928.

Observations were made on eight obese women, normal except for excess weight, who were reducing by measures of diet alone. The basal metabolism was determined at intervals of a few days to two weeks. In seven patients with normal metabolism, the increase in calories was 26 per cent above normal for the same persons if of ideal weight. This was not proportional to the weight excess, but was proportional to the increase of body surface. On reduction of weight, the caloric value dropped to 6 per cent above normal, even when the body weight remained 40 per cent above normal.

H. R. FISHBACK.

RENAL FUNCTION IN CHRONIC CARDIAC DISEASE WITHOUT SIGNS OF HEART FAILURE. H. J. STEWART and J. F. MCINTOSH, J. Clin. Investigation **6**: 325, 1928.

In thirty-five patients recently recovered from heart decompensation, renal function was tested by the following methods: (1) the urea concentration index; (2) the phenolsulphonephthalein test; (3) the concentration test, and (4) the dilution test. In ten patients, all four tests gave normal values. The urea concentration index was normal in all except eight patients, and the phenolsulphonphthalein excretion was subnormal in only one patient. The dilution test showed lessened water excretion, failure of the specific gravity to fall or both in seventeen patients, while ten patients showed diminished concentration power. Thus, the most frequent abnormality found was more or less fixation of the specific gravity of the urine. After the age of 30, or in patients with arteriosclerosis or hypertension, normal renal function was rarely found. There was no correlation between the duration of heart disease and the degree of impairment of renal function.

H. R. FISHBACK.

PROPERTIES OF THE GONADS AS CONTROLLERS OF SOMATIC AND PSYCHICAL CHARACTERISTICS. CARL R. MOORE, J. Exper. Zool. **50**:455, 1928.

By surgical removal of the testis from its epididymis in rats and guinea-pigs, the life and motility of spermatozoa remaining in the isolated epididymis have been studied under a variety of conditions.

In the isolated epididymis of the guinea-pig (opposite testis normal), spermatozoa remain alive and capable of motility on proper stimulation for seventy days, but with double epididymal isolation (both testes removed) this capacity for motility persists for but twenty-three days. In the rat comparable time intervals are thirty days and seventeen days. The greater length of life of spermatozoa when one testis is present, in contrast with the absence of all testis tissue, becomes an indicator for the presence of the testis hormone, since it follows under conditions when no spermatogenesis is present. This spermatozoon-motility test provides a dependable, easily read, purely objective test for the testicular hormone.

The temperature regulating influence of the scrotum is easily demonstrated by confining the isolated epididymis in the abdomen; the length of life of the spermatozoa under such conditions is greatly shortened.

The spermatozoon-motility test has been studied under such a variety of conditions as the following: as influenced by (1) early and later experimental cryptorchid testes; (2) macerated testis injections; (3) delayed removal of the testis hormone; (4) nonliving testis grafts; (5) living testis fractions.

The physiology of the epididymis has likewise been recognized in a new light.

AUTHOR'S SUMMARY.

A STUDY OF THE ADRENAL CORTEX IN THE MOUSE AND ITS RELATION TO THE GONADS. R. DEANESLY, Proc. Roy. Soc., London **103**:523, 1928.

The histologic difference between the suprarenal glands of male and female mice, reported by previous writers, has been further investigated. At the age of 3 weeks, the suprarenals are alike in the two sexes; in inner dark-staining cortical zone can be distinguished. Growth of this zone ceases in the male before the age of 5 weeks; a small amount of degeneration takes place, and fibrous reticular tissue develops around the medulla. In the female, this zone continues to grow until puberty; it then occupies more than half the cortex. Later, it degenerates slowly in the unmated animal, and normally disappears before the end of the reproductive period. The reduction of this zone is accompanied by a proliferation of fibrous tissue in the same region which persists after total degeneration has taken place. No correlation has been found between histologic changes in the gland of the unmated mouse and the estrual cycle. Complete degeneration of the inner zone of the cortex takes place between the seventh and twelfth days of pregnancy; the histologic changes occur more rapidly than those in the gland of the unmated female, but are otherwise identical with them. A new inner zone may arise later in the cortex; this, though similar to the earlier one, is distinguishable from it, but is also of a transitory character. The effect of castration on the suprarenal gland is to cause the growth of an inner cortical zone of the female type. Ovariotomy appears to have no effect on the suprarenal gland. The histology of the suprarenals in mice is discussed in relation to that of man and other mammals. Double suprarenalectomy was performed on a number of male and female mice which bred normally after the operation. It was found that the estrual cycle was slightly lengthened in unmated suprarenalectomized females, but otherwise was normal.

AUTHOR'S SUMMARY.

THE PHYSIOLOGY AND PHARMACOLOGY OF THE UMBILICAL CORD CIRCULATION. H. RUNGE, M. BAUER and H. HARTMANN, Arch. f. Gynäk. **134**:626, 1928.

Perfusion studies were carried on in portions of the placenta and the umbilical cord to obtain information regarding the physiologic and physiochemical part played by the cord circulation. The difference in the pressure of the arteries and the vein

of the umbilical cord amounted to about 50 per cent. The blood pressure of the cord vein was, nevertheless, higher than that of the somatic veins of the fetal body which is based on the mechanical power of the fetal heart. The umbilical vein is permeable to aqueous stains but not to colloidal stain material. The permeability increases with the proportion of pressure utilized. Neither aqueous nor colloidal stains could be filtered through the arteries. The relation of the permeability of the veins to the origin of the amniotic waters was then significantly discussed. The anatomic verification of the vessel permeability was found in the relationship of the surrounding Wharton jelly of the cord to the vein and arteries. The vein was intimately related to its surrounding substance, whereas this is more or less lacking in the umbilical arteries.

A. J. Kobak.

Sudden Death from Ventricular Fibrillation. W. Stepp and G. W. Parade, München. med. Wchnschr. **75**:1869, 1928.

Air in quantities of from 0.5 to 30 cc. of suspended carbon and oil, some emulsified, was injected into the left ventricle of dogs. There followed marked restlessness, dyspnea, rapid breathing and severe disturbances of the heart rhythm. Marked changes occurred in the electrocardiograms. Although ventricular flutter and fibrillation were noted, auricular fibrillation was not observed. Continuous ventricular fibrillation always occurred within seven minutes, but usually appeared within two or three minutes following the injection. In all experiments, the onset of ventricular fibrillation appeared from one half to one minute before respiration ceased. In the experiments without ventricular fibrillation, especially following air embolism, the death of the heart was slower and preceded by extrasystole and sinus tachycardia. The postmortem examination confirmed the results of Gundermann, in all experiments with ventricle fibrillation, i. e., a massive accumulation of air bubbles or carbon particles in the coronary arteries. Air bubbles and carbon particles were distributed also in the arteries of the brain and elsewhere. The presence of air or carbon particles in the coronary arteries, demonstrated in all experiments in which death resulted from ventricular fibrillation, leads to the conclusion that ventricular fibrillation is caused by a disturbance of the blood supply of the myocardium or of the conduction system. Certain clinical applications are discussed in conclusion.

Edwin F. Hirsch.

Pathologic Anatomy

Aneurysm of the Splenic Artery. E. L. Hunt, Am. J. M. Sc. **176**:195, 1928.

A case of this rare condition is described with autopsy observations. Besides the ruptured aneurysm, there were also arteriosclerosis, cardiac hypertrophy and pulmonary edema.

Pearl Zeek.

Addison's Disease in the Negro. L. S. Evans, Am. J. M. Sc. **176**:499, 1928.

This disease in negroes is probably more common than is generally supposed, but is difficult to diagnose because of the natural pigmentation of the skin. Three cases are reported, one with autopsy observations.

Pearl Zeek.

An Experimental Study of Arterial Collateral Circulation. H. E. Pearse, Jr., Ann. Surg. **88**:227, 1928.

The author removed the main portion of the femoral artery in dogs and found that gangrene did not develop, nor was there any functional disability. With the adoption of Hill's injection method, a rich anastomosing vascular network could be demonstrated in these limbs. Sections of the tissue did not reveal newly formed blood vessels. The presence of one or two lateral branches will prevent total atrophy of a segment of artery isolated between ligatures, and three or more will preserve such a segment intact. Vasa vasorum pass around the ligature, obstructing their artery and thus acting as collateral channels.

N. Enzer.

PRIMARY BILATERAL TUMORS OF THE TESTICLE. C. C. HIGGINS, Ann. Surg. **88**:242, 1928.

The author reports a case of bilateral primary embryoma of the testes.

N. ENZER.

MORPHOLOGICAL CHANGES IN EXOPHTHALMIC GOITER FOLLOWING THE USE OF LUGOL'S SOLUTION. C. ALEXANDER HELLWIG, Surg. Gynec. Obst. **47**:173, 1928.

Thirty exophthalmic goiters removed after Plummer's treatment were compared with thirty glands removed without previous iodine medication. Most of the observations described by Rienhoff could not be confirmed. After Plummer's treatment no changes in the vascularity and in the amount of fibrous tissue were found. The acini were neither round, smooth-walled nor of regular size and form. Neither was the epithelium flat or cuboidal nor were the nuclei small, irregular and pyknotic. A formation of adenoma-like tumefactions and colloid cysts visible with the unaided eye did not occur in the material. In 84 per cent of the glands removed after Plummer's treatment, the only definite difference, as compared with untreated glands, was found in the appearance of the colloid. The acini of these glands had more and higher concentrated content in spite of the fact that the hyperplastic character of the glands was not altered. These observations corroborate Albert Kocher's observation that most of the exophthalmic goiters removed after iodine medication show distinctly more stained colloid than those without. Therefore, if one regards the liquefaction of the colloid as the most characteristic feature of exophthalmic goiter, it is doubtful that the change in the amount and quality of the colloid which follows Plummer's treatment completely explains the clinical improvement. The fact that in this material there was improvement in four cases following the use of a compound solution of iodine but no appearance of thick colloid in the glands, and that in one case there was no improvement after treatment with iodine but a gland rich in concentrated colloid, suggests that this problem is much more complicated and will not be solved by the anatomic method alone.

AUTHOR'S SUMMARY.

POLYCYTHAEMIA IN THE RABBIT FOLLOWING OPERATIONS INVOLVING THE PERITONEUM. R. HOWARD MOLE, J. Path. & Bact. **31**:645, 1928.

Four different kinds of operative procedures involving the peritoneum of the rabbit are reported, carried out under ether or procaine hydrochloride anesthesia, in each of which, after a brief period of anemia, a condition of polycythemia results. The cause of the polycythemia is undetermined.

AUTHOR'S SUMMARY.

CAPILLARY PERMEABILITY IN ACUTE URANIUM NEPHRITIS. CAROLINE WHITNEY, J. Path. & Bact. **31**:699, 1928.

The permeability of capillaries is decreased after uranium poisoning. The decreased permeability is evident within from eighteen to twenty-four hours after the administration of the drug; therefore, it is probable that the effect on the capillaries is a direct effect rather than a secondary effect of the kidney degeneration. The state of decreased permeability persists throughout the period in which it is possible to produce edema by the administration of excess fluid.

AUTHOR'S SUMMARY.

THE PRODUCTION OF HYPERPLASIA IN THE ALVEOLAR EPITHELIUM OF THE LUNG OF THE RABBIT. J. S. YOUNG, J. Path. & Bact. **31**:705, 1928.

Active manifestations of proliferation in the epithelial cells lining the marginal alveoli of the lung of the rabbit can be produced by the intrapleural injection of an emulsion of liquid paraffin and bile salts, whereas liquid paraffin alone is

ineffective. Similar changes follow the injection of solutions of a variety of neutral salts; viz., sodium chloride, calcium chloride, strontium chloride and aluminum chloride. The epithelial reaction increases as the valency of the cation of the salt increases. The action of calcium ions is not abolished by sodium ions. The significance of physical factors in the genesis of the epithelial proliferation is discussed.

AUTHOR'S SUMMARY.

THE APPEARANCE OF DOUBLY REFRACTING SUBSTANCE IN FORMALIN-FIXED RABBIT'S TISSUES. J. B. DUGUID and J. MILLS, J. Path. & Bact. **31**:721, 1928.

Doubly refracting substances make their appearance in the tissues of certain organs, notably the liver, after their removal from the body. The appearance has been investigated in human, rabbit and mouse tissues. Fixation in formaldehyde delays and limits the development of these substances but does not permanently prevent it. No development is found in tissues which have been fixed in corrosive mercuric chloride, U. S. P., or in osmic acid. No development takes place in tissues which have been fixed in potassium bichromate, and with formaldehyde (formol-Müller) a slight development takes place. The development of the substances is dependent on the tissues being placed in an acid medium after fixation. The substances are considered to be fatty acids, formed by hydrolysis from the lipoids in the tissues. We have not succeeded in staining them. The distribution of the substances gives no reliable indication as to their exact site of origin in the tissues, because in any piece of tissue the distribution alters according to the treatment to which that particular piece of tissue has been subjected. The anisotropic substances which occur in the suprarenal gland were compared with those which develop in the liver. The two substances were found to be similar in their chemical reactions, and considerable evidence pointed to both as being results of postmortem changes in the tissues. Injections of cholesterol into the blood stream of rabbits before death did not affect the appearance or the amount of the doubly refracting substances developing in the livers or other organs of these animals. We conclude that, since doubly refracting substances so readily develop in the tissues after death, their presence is of little importance as evidence of the state of affairs during life.

AUTHOR'S SUMMARY.

BLOOD CHANGES AFTER SPLENECTOMY IN SPLENIC ANAEMIA, PURPURA HAEMORRHAGICA AND ACHOLURIC JAUNDICE, WITH SPECIAL REFERENCE TO PLATELETS AND COAGULATION. W. HOWEL EVANS, J. Path. & Bact. **31**:815, 1928.

In ten of eleven cases in which splenectomy had been performed, the platelets showed a considerable increase. In one case of purpura hemorrhagica, they failed to show any marked increase, while in one case of splenic anemia (Rosenthal's thrombocythemic type) they rose to a high level, which was persistently maintained until the death of the patient from mesenteric thrombosis. The clotting time showed a rough parallelism to the platelet level. The clot retraction seemed much more proportional to the platelet count. After splenectomy there seems to be no correlation between the immediate and transient rise of the granular leukocytes and the slower and more persistent rise of the platelets.

AUTHOR'S SUMMARY.

THE RELATION OF THE BLOOD PLATELETS TO THROMBOSIS AFTER OPERATION AND PARTURITION. R. Y. DAWBARN, F. EARLAM and W. HOWEL EVANS, J. Path. & Bact. **31**:833, 1928.

After operations and childbirth, and especially after cesarean section, the number of platelets in the blood begins to rise about the fourth day, increases to a maximum about the tenth day and thereafter falls slowly to the normal level. A diminution of platelets is associated with an increase, and an excess of platelets

with a shortening of the blood coagulation time. The time relations of clinical thrombosis and embolism are similar to those of the platelet reaction: they are most frequent about the tenth day after operation or childbirth. The platelets show no change after simple hemorrhage, anesthesia or stopping in bed and no constant variation in sepsis. The platelet reaction is excited by fractures, and a similar rise occurs during convalescence from acute lobar pneumonia. It is suggested that the feature which is common to the various stimuli which have been identified is tissue injury and the absorption of break-down products.

AUTHOR'S SUMMARY.

BONE-MARROW IN THE SUPRARENAL GLAND. K. KNABE, Centralbl. f. allg. Pathol. u. path Anat. **43**:57, 1928.

In a woman, aged 75, dying of cardiac failure, a red-brown nodule, 7 by 6 mm., was found in the cortex of the right suprarenal gland at autopsy. The mass was soft and sharply circumscribed, and on histologic examination all stages of erythropoesis and giant cells of the type found in marrow were seen in it. Three possible explanations are offered for the anomaly. First, a compensatory new formation of marrow; second, the development of marrow carried to the suprarenal gland by the blood stream, and third, a congenital heterotopy of marrow.

GEORGE RUKSTINAT.

THE LIPOIDS OF THE MYOCARDIUM. E. SEHRT, Centralbl. f. allg. Pathol. u. path. Anat. **43**:97, 1928.

A wide discrepancy exists in the results obtained by pure chemical and histochemical investigations of the cardiac lipoids. These lipoids are known to consist of about 20 per cent fats found for the most part in the intermuscular tissues, 0.07 per cent cholesterol esters and from 60 to 70 per cent unsaturated phosphatides. The latter are labile and do not stain by the ordinary methods. Five factors influence the results of staining: (1) the affinity of the stain for its solvent (alcohol); (2) the solubility of the lipoids in this solvent; (3) the solubility of the stain in the examined lipoids; (4) the question if the affinity of the sudan III for its solvent is greater or less than its affinity for the lipoid; (5) physicochemical combinations of fat with other bodies, such as water, which prevent the combination of the stain with the lipoid. From this it follows that a lipoid can be stained if it is not soluble in the histologic solvent and if the affinity of the sudan III is greater for the lipoid than for its own solvent. The method advocated to secure the best results is as follows: Thin frozen sections are cut from fresh tissue, dipped into distilled water and dried in air for one hour. Staining is then carried out in an alcohol acetone solution of sudan III for from two to three hours. After this the sections are quickly shaken in 65 per cent alcohol, washed in distilled water, counterstained in Delafield's hematoxylin, washed in water and embedded in glyceringelatin on a slide. By this method, the cardiac muscle is seen to be packed with fat droplets in both the longitudinal and the cross-striations. In addition, fine fibrillae can be seen connecting the fat droplets.

GEORGE RUKSTINAT.

CORPORA ARENACEA IN THE LUNG. D. HUSSEINOFF, Centralbl. f. allg. Pathol. u. path. Anat. **43**:481, 1928.

A man, aged 30, dying of sepsis and malarial coma, at autopsy had an extensive right fibrous pleuritis and in the center of the right lower pulmonary lobe a red, stony mass, the size of a hazelnut. In this were bodies resembling corpora amylacea, some of which were partially calcified. The vessels in the mass were involved in various stages of thickening and hyalinization, and those completely obliterated and occupied by concentric calcium deposits were regarded as corpora arenacea.

GEORGE RUKSTINAT.

FAMILIAL CONGENITAL MACROSOMIA ADIPOSA. T. CHRISTIANSEN, Hospitalstidende **71**:421, 1928.

Christiansen discusses the endocrine disorder designated by this name, seen in the children of two sisters with menstrual anomalies. Of nine children born at term, seven had macrosomia, five dying within the first year. Necropsy revealed adenomas in the suprarenal cortex and eosinophilia in the thymus. Congenital macrosomia is regarded as a suprarenal syndrome belonging to the obese type (Guthrie and Emery), due to a hyperepinephry (Apert), but distinguished by the absence of hirsuties and genital changes and in other ways from the suprarenal syndromes described in the literature to date.

THE CONNECTION BETWEEN THE HYPOPHYSIS AND THE MID-BRAIN. B. N. MOGILNITZKY, Virchows Arch. f. path. Anat. **267**:263, 1928.

The author exposed the brains of three dogs to roentgen rays, and found in all, besides atrophy of the glandular portion of the hypophysis, marked proliferation of glia cells and atrophy of the posterior lobe, also bilateral atrophic and degenerative changes in the nucleus supra-opticus and in the tuber cinereum. Degeneration of the tractus supraopticohypophyseus had apparently occurred as a result of the changes in the hypophysis.

B. R. LOVETT.

CHRYSOSIS IN RABBITS AND DOGS. H. BORCHARDT, Virchows Arch. f. path. Anat. **267**:272, 1928.

After injection of a gold preparation by various routes into animals, the metal could be demonstrated in bound form in all the organs. It was stored chiefly in the reticular cells of the liver and spleen, and was excreted through the kidneys. Metallic gold could also be demonstrated chemically in the cells after injection of a fine emulsion of the metal.

B. R. LOVETT.

MALFORMATION OF THE LEFT VENTRICLE. H. O. KLEINE, Virchows Arch. f. path. Anat. **267**:281, 1928.

After reviewing the literature, Kleine describes his case, in which a band was found resembling one of the chordae tendineae extending from the valve of the foramen ovale to the free border of the mitral valve between the two leaflets. It appeared to be a prolongation of the flap covering the foramen ovale. There were also three, instead of two, pulmonary veins.

B. R. LOVETT.

STENOSIS OF THE CONUS ARTERIOSUS AS A RESULT OF PARIETAL ENDOCARDITIS. G. LEITMANN, Virchows Arch. f. path. Anat. **267**:290, 1928.

Stenosis of the conus arteriosus was found following a mural endocarditis with fibrosis of the right ventricle.

B. R. LOVETT.

MALFORMATIONS OF THE ORGANS OF RESPIRATION. F. PAUL, Virchows Arch. f. path. Anat. **267**:295, 1928.

Three instances of malformations are described. In the first, the left lung was lacking and the pleural cavity was entirely filled by the pericardium and right lung. A rudimentary lung was attached to the esophagus. In the second case, an artery branched off from the aorta just above the diaphragm, and entered the lower lobe of the left lung. Its branches anastomosed with the left pulmonary artery. Extensive caseous tuberculosis was present, confined to the region supplied with blood from the aorta. The third case, that of a stillborn infant, revealed the upper end of the esophagus ending blindly, and the lower end attached to the trachea at the bifurcation. All three are attributed to a fault in the segmentation process, during the development of the lung from the foregut in early embryonic life.

B. R. LOVETT.

AN AMNIOGENOUS MALFORMATION OF THE SKULL AND BRAIN. F. FRITSCHEK, Virchows Arch. f. path. Anat. **267**:318, 1928.

In a stillborn infant, the calvarium was lacking, and the hemispheres consisted of two small rudimentary nodules. There were adhesions between the placenta and the right hemisphere, and also two bands which caused a split in the face and a deformity of the left arm. "Very little amniotic fluid" was reported at the birth.

B. R. LOVETT.

PATHOLOGIC HISTOLOGY OF THE CHOROID PLEXUS: I. ALTERATIONS WITH AGE. E. VON ZALKA, Virchows Arch. f. path. Anat. **267**:379, 1928.

II. ALTERATIONS IN DISEASE, ibid., p. 398.

Even under normal conditions, the epithelium of the choroid plexus may be many-layered and show extensive desquamation. The changes most frequently found are those connected with advancing age. These are: in the epithelial cells, vacuolization, pigmentation and flattening; in the connective tissue, diffuse and focal sclerosis, formation of cysts, psammomas and hyaline bodies, and calcification. These physiologic alterations must be considered before attributing changes to disease of the nervous system.

Marked hyperemia of the choroid plexus was found in a variety of conditions. Amyloid occurred as a part of general amyloidosis. Inflammatory changes, investigated chiefly in tuberculous meningitis, consisted of infiltration of the blood vessel walls and perivascular connective tissue with lymphocytes, epithelioid cells, leukocytes, occasional giant cells and nets of fibrin. Fibrinopurulent exudate was found between the villi in several cases. Leukocytic infiltration occurred in two cases of suppurative meningitis. In chronic inflammation, especially syphilis, there was increase of connective tissue around the vessels, with infiltration of plasma cells and lymphocytes. In leukemias the capillaries were seen to be distended with the corresponding type of cell. Tumors of the plexus are rare; one instance of benign papilloma was investigated. A connection between uremia and changes in the plexus is denied by the author, since the changes reported by others and found by him were largely increase in hyaline connective tissue, such as occurs physiologically with advancing age. No characteristic changes were associated with diabetic coma.

B. R. LOVETT.

INNERVATION OF THE VOLUNTARY MUSCLES. T. TSUNODA, Virchows Arch. f. path. Anat. **267**:413, 1928.

Different types of nerve-endings in the voluntary muscles were examined by a special staining method and described. The results indicated a double or triple efferent innervation of the muscle. Section of the nerve roots above the spinal ganglion was followed by wallerian degeneration of the medullated fibers, and no change in the nonmedullated ones. In the muscle bundle itself, half of the medullated nerve-endings degenerated while the other half remained intact. Section below the ganglion caused degeneration of all medullated nerve-endings. The author concludes that half of the medullated nerves are motor while the other half belong to the sensory nerves of the spinal ganglion. In beriberi in pigeons, marked degeneration of the axis cylinder of the nerve-endings was invariably found, swelling followed by atrophy. In nonmedullated fibers the changes were much less pronounced. Giving vitamin B improved the condition.

B. R. LOVETT.

CHANGES IN THE NERVE-ENDINGS OF THE SKIN IN BERIBERI IN BIRDS. T. TSUNODA and N. KURA, Virchows Arch. f. path. Anat. **267**:421, 1928.

In pigeons and ducks with beriberi, changes in the axis cylinders of the sensory nerves and their endings are in general those of cloudy swelling. Frag-

mentation or granular degeneration is not found. When one injects vitamin B into these animals, the clinical symptoms disappear. The sensory nerve-endings as well as the motor nerves return to the normal condition rapidly, within twenty-four hours. One may conclude that disturbances of the motor, sensory and sympathetic nerves go together in beriberi. The histologic changes in motor and sensory nerves are the same.

B. R. LOVETT.

Pathologic Chemistry and Physics

BLOOD CHEMICAL STUDIES IN ARTERIAL HYPERTENSION. RALPH H. MAJOR, Am. J. M. Sc. **117**:188, 1929.

In certain cases of hypertension, the blood is found to contain an increased amount of some substance giving the same color response as guanidine and having certain chemical properties like those exhibited by the guanidine bases.

PEARL ZEEK.

THE REACTION OF HUMAN BILE AND ITS RELATION TO GALL STONE FORMATION. JOHN G. REINHOLD and L. KRAAER FERGUSON, J. Exper. Med. **49**:681, 1929.

The human gallbladder acidifies the bile. In this respect its action is similar to that of the gallbladder of lower animals, previously described by other workers. The hydrogen ion concentration of gallbladder bile is increased considerably in cases of obstruction of the common or cystic ducts. The highest values were found following complete obstruction. The occurrence of gallstones was not associated with a consistent change in the hydrogen ion concentration of the gallbladder bile.

AUTHORS' SUMMARY.

GASTRIC SECRETION AND URINARY REACTION. DANIEL DAVIES, Brit. J. Exper. Path. **10**:1, 1929.

In cases of true achlorhydria the reaction of the urine is remarkably constant, and may afford not only an additional means of diagnosing the condition but may aid in distinguishing between true and false achlorhydria.

PEARL ZEEK.

THE PHOSPHORUS CONTENT OF THE BLOOD IN DIABETES MELLITUS. F. B. BYROM, Brit. J. Exper. Path. **10**:10, 1929.

In severe untreated diabetes and in diabetic coma there is a pronounced fall in the organic acid-soluble phosphorus of the blood corpuscles, which appears to be the result of acidosis. After satisfactory treatment by dietetic restriction and insulin, the ester phosphorus returns to the normal level. In fatal dabetic coma the inorganic phosphate rises considerably, probably as the result of renal damage.

PEARL ZEEK.

HYDRAULIC ACTION OF TISSUE FLUID. R. BENEKE, Beitr. z. path. Anat. u. z. allg. Path. **79**:166, 1927.

Beneke discusses at considerable length the rôle of the physico-mechanical action of tissue fluid in the normal and pathologic formation of connective tissue. Since water is inelastic and noncompressible, the tissue fluid has the property of transmitting to the cells embedded in the fluid all mechanical impulses and shocks. Normal mechanical impulses to which the body is constantly subjected are those of the pulse wave and of body movements. The effect of such impulses transmitted to cells suspended in a fluid or semifluid matrix would be to disrupt the cellular elements. The latter are protected against the hydraulic action of the tissue fluid by the collagenous connective tissue fibers which are laid down between the

cells and which take up and dissipate the shock of mechanical impulses. Beneke takes the teleologic point of view that not only does the connective ground substance protect the cells against shock, but that it is laid down to have this protective action as the result of mechanical impulses. It is thus that he accounts for the formation of normal connective tissue in general and for the special arrangement of the connective tissue of the cardiovascular system and of the dura. He then takes up seriatim a number of pathologic connective tissue overgrowths, which are interpreted as the result of abnormal hydraulic impulses, the purpose of the overgrowths being to protect the surrounding tissues from the abnormal shocks; thickening of the endocardium and of the artery wall; elephantiasis; condensation and fibrillation of the crystalline lens and fibrosis about the auditory labyrinth; thickening of the tunica vaginalis, peritoneum and pleura in hydrocele, ascites and pleural effusion; subependymal gliosis and fibrosis of the choroid plexus in chronic hydrocephalus; the formation of the host capsule about achinococcus cysts; the formation of the fibrous wall of neoplastic cysts; the encapsulation of areas of cerebral softening and hemorrhage. The idea is called on to explain even the formation of tumors of the brain, in the causation of many of which Beneke thinks trauma is a factor; the trauma leads to liquefaction or hemorrhage of brain tissue. If the fibrous capsule, which is formed about the liquefied area as the result of hydraulic shocks transmitted by the fluid, is inadequate to protect the surrounding brain tissue, then a tumor may result from the insult of constantly recurring shocks. Since the article is dedicated to Abderhalden, on the occasion of the latter's fiftieth birthday, the author may be pardoned for likening the formation of connective tissue fibrils in a fluid matrix to the precipitation of fibrin through enzyme action, and for considering the process of protective mechanism akin to the immunity reaction.

O. T. SCHULTZ.

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY. P. FREUDENTHAL, Virchows Arch. f. path. Anat. **266**:640, 1928.

A case is described and explained according to Spitzer's theory of reversion to a phlyogenetically older step in the development of the heart.

B. R. LOVETT.

Microbiology and Parasitology

ANTI-STAPHYLOCOCCIC EFFECTS OF THE INTRA-ARTERIAL INJECTION OF CERTAIN DYES. Z. D. ZAU and F. L. MELENEY, Ann. Surg. **88**:961, 1928.

The effect of mercurochrome-220 soluble, gentian violet and acriflavine on tissues and on infection was studied by injection into the aorta and the femoral artery of dogs. In fourteen dogs lesions were produced by hemolytic staphylococci, and there was no evidence that the injection of dye twenty-four, forty-eight and seventy-two hours after the injection of the organisms had any effect on the course of the infections. The work is significant, showing that these dyes may be injected intra-arterially without damage to the arteries, and also because of damage to the kidney and liver when the injections were made intra-arterially in doses from 1 to 16 mg. per kilogram of body weight. It is concluded that the failure of the administration of this dye by way of the arteries to act on the infection implies that an intravenous injection of the same quantity would hardly be efficacious.

N. ENZER.

AN INVESTIGATION OF STREPTOCOCCI ISOLATED FROM THE ALIMENTARY TRACT OF MAN AND CERTAIN ANIMALS. J. M. ALSTON, J. Bact. **16**:397, 1928.

There is a clearly defined group of organisms sufficiently differentiated to be classified together as enterococci. Like many other bacteria, there are atypical varieties which are intermediate between the typical ones and the closely related varieties. We would specify the attributes which justify the inclusion of an organ-

ism in the enterococcus group as follows: cocci tending to be oval and occurring in pairs or short chains, heat resistant up to 60 C. for ten minutes, and nonhemolytic and capable of fermenting mannitol, as secondary and not invariable characters. Among fifty-one strains of streptococci isolated from the alimentary tract of man, dog and rat, sixteen (31 per cent) conformed to the description of enterococci (Dible). The remainder of the streptococci isolated from feces or intestine, with one exception, grew on a bile-salt medium and were nonmannitol fermenters and heat sensitive, and showed the sugar reactions of *Streptococcus mitis* (Holman). Six streptococci obtained from the mouth or stomach and one obtained from the duodenum did not grow on a bile-salt medium and were of the type of *Streptococcus mitis, S. salivarius* or *S. nonhemolyticus III* (Holman).

AUTHOR'S SUMMARY.

ATTEMPT TO CULTIVATE BACTERIA FROM RABBIT ENCEPHALITIS VIRUSES. FEI-FANG TANG and M. RUIZ CASTANEDA, J. Bact. **16**:431, 1928.

The experiments failed to show any causal relationship between the ordinary visible bacteria and encephalitis and furnished no evidence to support the suggestion that the filtrable encephalitis virus may change into a true bacterial form.

AUTHORS' SUMMARY.

FILTRATION OF THE VIRUS OF HERPETIC ENCEPHALITIS AND OF VACCINIA. HUGH K. WARD and FEI-FANG TANG, J. Exper. Med. **49**:1, 1929.

The virus of herpetic encephalitis and the virus of vaccinia can be demonstrated in the filtrate, if a broth emulsion of fresh tissue containing the virus is passed through a Berkefeld filter.

AUTHORS' SUMMARY.

THE GERMICIDAL AND HEMOLYTIC ACTION OF A-BROM SOAPS. ARNOLD H. EGGERTH, J. Exper. Med. **49**:53, 1929.

The soaps of the a-brom fatty acids are usually more germicidal than the unsubstituted soaps. Only when *B. typhosus* was the test organism was there no increase in germicidal action. For any test organism, germicidal action of the brominated soaps increases rapidly with increasing molecular weight up to a certain point, then diminishes. This is likewise true of the hemolytic titer. The point of maximal germicidal action varies with the different species of test organisms. In the series studied, brominated soaps of 12 and 14 carbon atoms were most germicidal for the gram-negative organisms, while soaps of 16 and 18 carbon atoms were most germicidal for gram-positive organisms. The brominated soaps are, in general, more active in acid than in neutral or alkaline reactions. The reasons for this have been discussed in a previous paper, in which a similar phenomenon with unsubstituted soaps was observed. For certain organisms, the brominated soaps are among the most rapid and potent germicides known.

AUTHOR'S SUMMARY.

FOWL PARALYSIS (NEUROLYMPHOMATOSIS GALLINARUM). ALWIN M. PAPPENHEIMER, LESLIE C. DUNN and BERNON CONE, J. Exper. Med. **49**:63, 1929.

Fowl paralysis is a disease entity, with characteristic clinical and pathologic features. The disease occurs in all parts of the United States, Holland, Austria and probably South America. The disease appears to be endemic in certain foci. Having once appeared, the disease tends to persist through successive years. It occurs with about equal frequency in both sexes; all common breeds may be affected. Symptoms appear between the third and eighteenth months. Typical clinical cases have not been observed outside of these limits. The conspicuous symptoms are asymmetrical, partial and progressive paralysis of the wings and both legs, and rarely of the muscles of the neck; occasionally, gray discoloration of the iris, with blindness. Nutrition is usually preserved. The duration is vari-

able; the outcome is usually fatal, but spontaneous recovery may rarely occur. The principal pathologic changes are found in the nervous system. In the peripheral nerves, the essential feature is an intense infiltration of lymphoid, plasma cells and large mononuclears. This is accompanied by a myelin degeneration in the more advanced lesions, but the cellular infiltrations appear to precede the degenerative changes. In the brain, cord and meninges, there are similar infiltrations predominantly perivascular. Infiltrations of the iris with lymphoid and plasma cells are found in the cases showing gross discoloration of the iris. Visceral lymphomas, originating usually in the ovary, are associated in a certain percentage of the cases. Evidence is presented in favor of the view that this association is not accidental, and that the lymphomas are a manifestation of the disease. Infiltrations of the spinal cord and brain, rarely of the peripheral nerves, are frequently present in birds showing no clinical symptoms. These are interpreted as mild cases of the same disease. No micro-organisms of etiologic significance have been demonstrated in the tissues or by cultural methods.

AUTHORS' SUMMARY.

TRANSMISSION EXPERIMENTS WITH FOWL PARALYSIS (NEUROLYMPHOMATOSIS GALLINARUM). ALWIN M. PAPPENHEIMER, LESLIE C. DUNN and S. M. SEIDLIN, J. Exper. Med. **49**:87, 1929.

Inoculation of suspensions of brain, cord, ganglions or nerves of chickens with neurolymphomatous lesions into newly hatched chicks is followed by the development of typical lesions in approximately 25 per cent of cases. In control chickens kept under laboratory conditions, the incidence of the disease is about 7 per cent. The disease does not become manifest until at least two months after inoculation; symptoms may not appear until after four months. The active agent is not destroyed by 50 per cent glycerol in nine days at icebox temperature.

AUTHORS' SUMMARY.

THE PATHOGENICITY OF THE AVIAN TUBERCLE BACILLUS. ELISE S. L'ESPERANCE, J. Immunol. **16**:27, 1929.

The results obtained in this series of experiments seem to indicate that it is possible to transform an animal relatively resistant to the avian tubercle bacillus into a more or less susceptible one, by previous treatment with a dead heterologous strain of tubercle bacilli.

AUTHOR'S SUMMARY.

EXPERIMENTAL INOCULATION OF CHICKENS WITH HODGKIN'S NODES. ELISE S. L'ESPERANCE, J. Immunol. **16**:37, 1929.

In chickens, a lesion with the histologic features of Hodgkin's granuloma, and comparable to avian tuberculosis, has been produced after the inoculation of emulsified Hodgkin's nodes. This may indicate that the etiologic agent in certain forms of Hodgkin's disease is pathogenic for birds, or that the avian tubercle bacilli are a factor in producing some of the lesions which are interpreted as Hodgkin's disease.

AUTHOR'S SUMMARY.

THE BROAD TAPEWORM IN AMERICA WITH SUGGESTIONS FOR ITS CONTROL. TEUNIS VERGEER, J. Infect. Dis. **44**:1, 1929.

The history of the broad tapeworm in America is briefly reviewed. The possibility of finding several other larval forms of the tapeworms of man in fishes is pointed out, and the necessity is stressed of rearing larval forms to adults for the purpose of identification. *Dibothriocephalus latum* is nearly world wide in its distribution. The life cycle, which is discussed, is not completely known. The plerocercoids are described and figured to aid in identification. It is demonstrated that fishes from all commercially important lakes in Canada are infested with the larval forms of *D. latum*. Prophylaxis is discussed.

AUTHOR'S SUMMARY.

EFFECT OF OXYGEN ON THE VIABILITY OF YOUNG CULTURES OF CLOSTRIDIUM BOTULINUM. GAIL M. DACK and ELIZABETH H. WILLISTON, J. Infect. Dis. **44**:27, 1929.

The viability of young cultures of *Clostridium botulinum* type A and type B exposed to oxygen for periods of from thirty seconds to one hour was greatly reduced. Only a small percentage of the organisms demonstrated by the hemacytometer count were viable.

The age of the culture is one factor determining the resistance of the cells to oxygen, the younger (twelve-hour) cultures being more sensitive than the older (forty-eight hour) ones. The type of menstruum in which the cells are suspended alters their resistance to oxygen. The number of cells surviving treatment with oxygen in salt solution is small, while if a phosphate buffered salt solution is used the viability is greater.

AUTHORS' SUMMARY.

INFECTIONS OF THE UPPER RESPIRATORY TRACT AND MIDDLE EAR. JOHN H. FISHER, J. Infect. Dis. **44**:33, 1929.

The pathogenicity of the organisms isolated from fifteen cases of infection of the middle ear in man was tested in rabbits by intranasal inoculations. The nasal passages of the rabbits were previously swabbed with a 50 per cent aqueous solution of phenol. Eleven of these rabbits died, and in each case acute purulent paranasal sinusitis and acute otitis media were found. From these lesions, in each instance, an organism similar to the type inoculated was recovered. Associated lesions, in some of the rabbits, were acute pleuritis and empyema, lobular pneumonia, abscesses of the lung, acute pericarditis and septicemia. From these lesions, in each case, organisms similar to those inoculated intranasally were recovered. The experiments were controlled by two groups of rabbits, one group receiving culture only, intranasally, the other receiving swabbing only. None of the rabbits of these two groups died. Some factor which lowers the resistance of the nasal mucosa is necessary for the infection of the upper respiratory tract and middle ear. In twelve untreated normal control rabbits there was no evidence of otitis media.

It is thought that the use of 50 per cent phenol as a means of reducing resistance of tissue may prove of value in the experimental infection of animals.

Fifty cases of acute infection of the middle ear in man were studied bacteriologically. *Streptococcus hemolyticus* was the exciting organism most frequently found, while *Staphylococcus* and *Pneumococcus* were next.

The evidence indicates that otitis media is not blood-borne, but develops by direct extension from an infection of the upper respiratory tract.

AUTHOR'S SUMMARY.

YEASTLIKE ORGANISMS OF HUMAN ORIGIN. MARGARET J. MCKINNEY, J. Infect. Dis. **44**:47, 1929.

Many of the yeastlike organisms occurring in routine hospital culture may be the etiologic factor of the pathologic condition under examination since eleven of twelve strains studied were virulent. One strain was avirulent for both guinea-pigs and rabbits, although it had been repeatedly isolated from the stools of a patient with chronic colitis.

Culturally, the yeastlike organisms were *Monilia,* producing mycelium and having no ascospores. They were only distantly related to the gram-positive budding organism from Fleischmann's yeast. Identification of the yeasts according to the table of biochemical characters given by Castellani was difficult, since they differed in one or more cultural reactions from those in his classification.

Immunization of animals with the organisms produced serums high in agglutinins and complement-fixation antibodies. The agglutination and complement fixation indicated a marked difference between Fleischmann's yeast and *Monilia* from human sources. One strain was more closely allied to Fleischmann's yeast in its

immunity reactions than to the pathogenic strains. With the exception of those of Fleischmann's yeast, the agglutinin and complement-fixation reactions showed only slight group or species specificity. In the small group of yeastlike strains studied, there was no clear correlation between the source, the cultural characteristics and the serologic reactions.

AUTHOR'S SUMMARY.

THE TRANSMISSION OF BARTONELLA IN ALBINO RATS. PAUL R. CANNON and PRESTON H. MCCLELLAND, J. Infect. Dis. **44**:56, 1929.

The anemia following splenectomy in albino rats is due to a virus which is transmissible from rat to rat by inoculation of the parenchyma of the liver or by the blood. This infection is spread by contact of uninfected rats with infected ones. Lice from infected rats can convey the virus to uninfected rats. The infection is not readily spread by contact if the infected rats are completely freed from ectoparasites, particularly lice. The virus is presumably *Bartonella muris*. The mode of transmission indicates that the bartonella of Oroya fever may be transmitted similarly by the body louse (*Pediculus corporis*) or the bedbug (*Cimex lectularius*).

AUTHORS' SUMMARY.

"SMOOTH-ROUGH" VARIATION IN BACTERIA IN ITS RELATION TO BACTERIOPHAGE. F. M. BURNET, J. Path. & Bact. **32**:15, 1929.

There are characteristic differences in the behavior of the smooth and rough forms of *Salmonella* strains toward bacteriophage. Certain phage types are limited in their action to smooth forms, others attack only rough strains, while a third group may lyse either form. The type of resistant colony produced is related to these characteristics of the lysing phage. "Smooth" phages tend to give rough or partially rough resistants, "rough" phages with certain rough cultures provoke the appearance of true smooth forms, while those phages which lyse both forms impartially are more liable to show specifically resistant forms in the same phase as the parent strain. From cultures that are rough by all the usual criteria, it is possible by the use of suitable phages to derive true smooth forms showing all the characters of the type including active virulence. Some rough cultures could not be so converted to the smooth type, and the evidence, which is incomplete, suggests that the conversion can occur only so long as a trace of smooth antigen is retained in the antigenic make-up of the bacillus. The quantitative relations between the numbers of bacilli lysed and the numbers of the various types of resistant colonies strongly suggest that the appearance of a new phase (R or S) under the influence of phage is purely a selection phenomenon. Experiments are presented to disprove Bail's contention that phages which produce the same type of resistance with a single bacterial strain are necessarily qualitatively identical. A general discussion of the nature of bacterial resistance to phage is attempted from the standpoint that its most important factor is change in the bacterial constituent which also functions as the "heat-stable antigen."

AUTHOR'S SUMMARY.

BACTERIUM MORGANI FROM THE MAMMALS, BIRDS AND REPTILES. REGINALD LOVELL, J. Path. & Bact. **32**:79, 1929.

B. morgani was isolated from one bird, four monkeys and four reptiles, in circumstances which suggest this organism was etiologically related to the infection from which they died. No evidence was obtained that *B. morgani* is capable of producing a soluble exotoxin.

AUTHOR'S SUMMARY.

INTESTINAL BACILLI WITH SPECIAL REFERENCE TO SMOOTH AND ROUGH RACES. BRUCE P. WHITE, J. Path. & Bact. **32**:85, 1929.

The soluble specific substance may be extracted quantitatively from *Salmonella* and similar bacilli by hot dilute acid. Rough variants give an immediate reaction

with Millon's reagent; smooth races react only when the soluble specific substance has been removed. Under ordinary circumstances of test, smooth *Salmonella* and related bacilli and filtrates of broth cultures thereof are more toxic to laboratory rodents than are the corresponding rough bacilli and filtrates; the rough bacilli, however, possess a potential toxicity, disclosed by treatment with alcohol, approximating to that of the smooth forms. Mucoid growth in *Salmonella* has no relation to smoothness and is not analogous to capsule formation. The serologic reactions of rough variants appear to form a useful basis for a natural classification of intestinal bacilli.

AUTHOR'S SUMMARY.

GENERALIZED VACCINIA IN RABBITS WITH INTERNAL LESIONS. S. R. DOUGLAS, WILSON SMITH and L. R. W. PRICE, J. Path. & Bact. **32**:99, 1929.

A condition of experimental generalized vaccinia in rabbits is described which closely resembles human smallpox of the alastrim type. In this generalized disease almost every tissue of the body may be affected with the production of macroscopic lesions; no injury or irritation is necessary. The internal viscera most commonly affected are the lungs, liver, spleen, adrenal glands and the organs of reproduction. The kidneys are exceptional in that they have never shown generalized lesions. The mesodermic origin of an organ does not indicate a nonsusceptibility to vaccinia. A strain of testicular passage virus was obtained which was highly infective when introduced by intraperitoneal inoculation; it produced a vaccinial peritonitis and gave rise to pathologic lesions in organs hitherto thought to be nonsusceptible, for instance, in the uterus, bladder, peritoneum and muscle. Vaccinia virus may remain latent in the tissues of an immune animal for a long period (up to at least forty-one days) after infection. Virus was recovered from the blood of an animal six days after infection. Infectivity of the blood is irregular and appears to have no correlation with the time incidence of generalization. Vaccinal infection caused abortion in three pregnant rabbits in all of which there was particular localization of lesions in the uterus. Both placenta and fetus contained virus.

AUTHORS' SUMMARY.

THE POSSIBILITY OF AN ABACILLARY BUT VIRULENT STAGE IN THE LATENT PERIOD OF TUBERCULOSIS. H. DURAND, P. KOURITSKY and R. BENDA, Compt. rend. Soc. d. biol. **99**:30, 1928.

Durand and his co-workers observed a patient with clinically latent tuberculosis whose sputum after being thoroughly examined, was injected into guinea-pigs and caused the death of the animals within a period of from eighteen, twenty-five, twenty-eight to thirty days, respectively. The tuberculous lesions found in these animals were confined only to the lymph nodes and closely resembled those lesions found in guinea-pigs after inoculation with the tuberculous filtrable virus. There was no ulcer at the point of inoculation. Moreover, the filtrate from the same sputum led rapidly to an atypical tuberculosis in the guinea-pig. Later on, when the sputum showed the presence of tubercle bacilli and this was injected into the guinea-pig, the animal showed the usual type of tuberculosis. The authors think that in the antebacillary period tuberculous patients expectorate an "invisible" but active tuberculous virus.

B. M. FRIED.

TWO CASES OF HUMAN INFECTION WITH BACILLUS ABORTUS. S. LEGEZYNSKY, Compt. rend. Soc. de biol. **99**:919, 1928.

The cases reported occurred in two veterinary physicians who came in close contact with sick cows. In one patient, the general symptoms were preceded by a furunculosis of the hand which assisted the abortion. The incubation period lasted from four to eight weeks. The outstanding clinical symptom was intermittent fever, which lasted six weeks in one patient; in the other there occurred two attacks at an interval of four weeks, each lasting fifteen days. The complement-fixation reaction and the agglutination test (1:1,600) were positive with the

abortus bacillus as well as with the Mediterranean fever micrococcus; the urine was negative for organisms, and the blood culture done after the fever subsided was sterile. The author affirms that Malta fever is entirely ignored in Poland, while the disease of the epizootic abortion is common. This fact plus the obvious exposure of the patients is definite proof that the veterinary physicians were infected with Bang's bacillus.

B. M. FRIED.

THE FILTRABILITY OF THE PFEIFFER BACILLUS. R. DUJARRIC DE LA RIVIERE, Centralbl. f. Bakteriol. **106**:30, 1928.

The author injected cultures of the Pfeiffer bacillus intraperitoneally into guinea-pigs and observed granular forms in the peritoneal exudate at the end of an hour. This exudate was then filtered through Berkefeld and Chamberland L2 bougies at a pressure of from 20 to 30 mm. of mercury. Before and after the filtration, tests were made to determine the viability of the Pfeiffer bacilli. The filtrate was inoculated into blood and vitamin broth. In fourteen of sixty filtrations the results were positive, Pfeiffer's bacilli being found in the filtrate. The suggestion is made that these observations may serve to harmonize the views as to a filtrable virus and the Pfeiffer bacillus being the cause of influenza.

PAUL R. CANNON.

THE PFEIFFER BACILLUS IN POSTMORTEM MATERIAL WITH ESPECIAL REFERENCE TO EPIDEMIC-FREE PERIODS. KARL LIEBER, Centralbl. f. Bakteriol. **106**:190, 1928.

Cultures of the trachea and bronchi of fresh cadavers were made in the effort to determine how frequently the Pfeiffer bacillus is present in nonepidemic as compared with epidemic periods. During the interval when grip was frequent, positive cultures for the Pfeiffer bacillus were frequently obtained; when warm weather appeared and grip disappeared, no positive cultures for the Pfeiffer bacillus were obtained in ninety-two consecutive necropsies. With the reappearance of cold weather and an increased incidence of grip, positive cultures were again secured, in one instance from the spinal fluid of a child with meningitis. The author concludes that the Pfeiffer bacillus regularly accompanies an influenza epidemic and in general, in epidemic-free periods, is not present.

PAUL R. CANNON.

"CENTRODERMOSES" WITH REFERENCE TO THE ETIOLOGY OF MEASLES. B. LIPSCHÜTZ, Virchows Arch. f. path. Anat. **267**:233, 1928.

Lipschütz classes measles with German measles, pityriasis rosea and lichen planus, as a "centrodermosis," meaning a skin disease characterized by pathologic changes in certain types of cells. Cytologic study of the eruption revealed characteristic pathologic types of "microcenters" in the histiocytes and epithelial cells in the region of the macules. Cells showing these abnormal bodies, centrocytes, were found constantly both in human material and in the skin of monkeys with experimentally produced measles. The author believes these changes to be due to the presence of an ultramicroscopic, filtrable virus in the skin.

B. R. LOVETT.

THE STABILITY OF VIRULENT STREPTOCOCCI. H. DOLD and H. R. MÜLLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:214, 1928.

Streptococci of different virulence which had been kept for from eleven to thirteen months on artificial mediums were studied. A streptococcus strain of low virulence (type I) showed after seventy-two subcultures no change in its degree of virulence. An increase of virulence could not be accomplished by twelve animal passages. Two streptococcus strains of moderate virulence (type II) showed some decrease of virulence after they were subcultured for several months

on artificial mediums. The original degree of virulence, however, could be restored by from three to five animal passages. A highly virulent strain showed toward the end of the experimental period some weakening in virulence. Three animal passages were not able to restore completely the previous high degree of virulence. It is concluded that the strains studied showed a marked tendency to preserve their original degree of virulence.

W. C. HUEPER.

THE VARIABILITY OF PNEUMOCOCCI. F. NEUFELD and W. LEVINTHAL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:324, 1928.

The degree of virulence of pneumococci can be preserved for years by growing them at 25 C. with subcultures every other day. Virulent pneumococci of type I in broth containing rabbit kidney kept at 37 C. are transformed after the third day into an avirulent form. The same change takes place in broth containing rabbit spleen while pneumococci grown in ordinary broth die after from two to three days. The addition of boiled kidney tissue keeps the pneumococci alive in an unchanged state for about six weeks. The experiments of Griffith are confirmed. An avirulent R-variety of type I injected into mice together with killed S-cocci changed into a typical virulent pneumococcus.

W. C. HUEPER.

ON THE BLOOD PICTURE AND HEMATOPOIETIC ORGANS IN EXPERIMENTAL RAT-BITE FEVER IN GUINEA-PIGS. Y. ISHIZU, Sc. Rep. Gov't Inst. Infect. Dis. **6**:267, 1927.

Experimental rat-bite fever in guinea-pigs produced a leukocytosis with a relative and absolute decrease in the lymphocytes and an increase in the number of pseudo-eosinophilic leukocytes and monocytes. The red blood cells and hemoglobin decreased together often with anisocytosis, poikilocytosis and basophilic stippling of the erythrocytes. The spleen was usually enlarged.

E. P. JORDAN.

Immunology

ASTHMA IN CHILDREN. M. M. PESHKIN and A. H. FINEMAN, Am. J. Dis. Child. **37**:39, 1929.

Each of eighteen children with asthma, ranging in age from 7 months to 14 years, were tested by the direct and indirect methods with thirty-three protein extracts, both the scratch and intradermal technics being used. Dry powdered extracts were employed for the scratch tests, and routine fluid extracts for the intradermal. All of these children were under observation for two years. The indirect method of testing (scratch and intradermal technics) employed as a routine measure to determine etiologic sensitizations in children with allergy is unsatisfactory. Its employment as a substitute for the direct method of testing even in specially selected cases is not practical.

AUTHORS' SUMMARY.

B. WELCHII ANTITOXIN IN TOXEMIA OF INTESTINAL OBSTRUCTION. J. J. MORTON and S. J. STABINS, Arch. Surg. **17**:860, 1928.

Jejunal obstruction 10 inches (25 cm.) below the ligament is fatal in dogs in from three to ten days. Death is preceded by manifestations of a toxemia associated with changes in the chemistry of the blood, chiefly of the chlorides and nonprotein partition. If the obstruction is relieved after the toxemia has developed, the condition is fatal. Some animals, however, recovered when *B. welchii* antitoxin was given intravenously. There is evidence that this antitoxin delays the onset of the toxemia. Other antitoxic serums did not have any influence on the outcome.

N. ENZER.

DISTRIBUTION OF AGGLUTININ IN THE LIVER AND THE LEG. JULES FREUND and CAROLINE E. WHITNEY, J. Immunol. **16**:109, 1929.

When rabbit serum containing agglutinins is injected into the vein of the ear in rabbits, agglutinins accumulate in the lymph of the liver rapidly, and in the lymph of the leg slowly. In immunizing animals passively, the titer of the lymph of the liver (obtained by cannulating a lymph vessel) may be as high as from 10 to 15 per cent of the titer of the serum within five minutes, and from 42 to 50 per cent within thirty minutes, after the injection of antibodies. The titer of the lymph of the leg is less than 10 per cent of the titer of the serum even six hours after passive immunization. When the accumulation of antibodies in the lymph is completed, the average of the titer of the lymph of the liver (75 per cent) is about twice as high as that of the lymph of leg (35 per cent). The rate of accumulation of antibodies in the passively immunized rabbit is rapid in the tissue of the liver and considerably slower in the muscles of the leg. The accumulation is completed in the liver within ten minutes; it continues for hours in the muscles of the leg. Perfusion of immunized rabbits in vivo or of the isolated liver reduces the agglutinin content both in the tissue and in the lymph of the liver. In the liver and in the muscle of the leg the parallelisms found between the tissues and their lymph, both as regards the rate of accumulation of agglutinins and the amount of agglutinins finally accumulated, are in harmony with the view that the agglutinins recoverable from tissues are the antibodies of the lymph, i. e., of the intercellular tissue fluid.

AUTHORS' SUMMARY.

ON THE RACIAL DISTRIBUTION OF SOME AGGLUTINABLE STRUCTURES OF HUMAN BLOOD. K. LANDSTEINER and PHILIP LEVINE, J. Immunol. **16**:123, 1929.

Correlating all the known facts it is uncertain whether one will succeed in discovering immunologic qualities entirely specific for races analogous to the characteristics of the serologic species; one is rather led to the idea that the serologic make-up of races is determined by varying combinations of a number of characteristics.

AUTHORS' SUMMARY.

VITAL STAINING WITH TRYPAN BLUE IN SHOCK IN RABBITS AND GUINEA-PIGS. SUSAN GRIFFITH RAMSDELL, J. Immunol. **16**:133, 1929.

For the rabbit, the tissues of importance in the absorption of trypan blue from the circulation during shock were found to be the skin, the mucous membranes, the blood vessels and the liver. For the guinea-pig, the only tissue of importance was the skin. Since the appearance of the dye in the tissues is assumed to be only an indication of edema, one may conclude that such a change can play no significant part in acute shock in the guinea-pig, and that in the rabbit its effects are only indirect, producing the toxic rather than the acute syndrome usually manifested by this animal. This does not mean that the first effect of an antigen antibody reaction is not on the capillary endothelium. Possibly the ensuing permeability is the first step in a stimulation of the smooth musculature so great, in the guinea-pig, as to obscure the less spectular edema, especially since the latter depends for its manifestation in a large measure both on the factor of time and on a special type of tissue that is rich in capillaries and connective tissue, which finds its highest development only in the skin.

AUTHOR'S SUMMARY.

THE RETICULO-ENDOTHELIAL SYSTEM AND ANTIBODY PRODUCTION. EDWARD F. ROBERTS, J. Immunol. **16**:137, 1929.

Evidence derived from a study of the effect of a reticulo-endothelial blockade in rabbits on the appearance of antibody in the circulating blood intimates a trend toward the inhibition of the rate and extent of the appearance of hemolysin, agglutinin and precipitin. The relative inefficiency of the method of so-called blockade and the factor of individual variation do not warrant the formulation

of definite conclusions from experiments of this kind. In addition to the predominant factor of individual variation among rabbits, the type of blockading agent, the dosage of the blockading agent, and the type of antigen are factors which account in large part for the diverse results reported in the literature.

AUTHOR'S SUMMARY.

COMPLEMENT FIXATION REACTION WITH RABIES AND HERPES VIRUSES. FEI-FANG TANG and M. RUIZ CASTANEDA, J. Immunol. **16**:151, 1929.

Despite repeated attempts, the work of Takaki, Kraus and their co-workers could not be confirmed, and no evidence could be found that there are specific complement-fixing antibodies in the serum of rabbits immunized against the viruses of herpes and rabies.

AUTHORS' SUMMARY.

IMMUNIZATION AND THE NITROGENOUS CONSTITUENTS OF THE BLOOD. M. F. GUYER and S. LEPKOVSKY, J. Immunol. **16**:175, 1929.

When a foreign protein such as that in the vaccine of *Bacillus typhosus* is injected into the blood stream of rabbits there results in general: a tendency toward diminution in the aminonitrogen content of the blood (except in moribund animals); a striking rise in nonprotein nitrogen; an increase in urea output, but scarcely enough to account for the full excess of nonprotein nitrogen; generally an obvious rise in the number of white blood cells; usually an elevation in temperature; lowering of the alkaline reserve; a lowering of the p_H which, in certain moribund animals, at least, along with the lowered alkaline reserve indicates an uncompensated acidosis; a rather prolonged inhibition of kidney secretion; a lowered specific gravity of the blood when water is administered, due to water retention; and in some cases a temporary acidosis of the body tissues.

That the results are due mainly to the foreign protein rather than to the ensuing fever is indicated by the fact that animals made febrile by infra-red radiation do not show the effects exhibited by the animals given injections of typhoid vaccine, although hemin has a tendency to produce the same changes in nonprotein nitrogen, urea nitrogen and the retention of urine. Apparently the aminonitrogen is deaminized in part, with reappearance of the nitrogen in urea. The lowered specific gravity of the blood when water is given by stomach tube, indicating dilution, is probably insufficient to account for all the water that had been administered prior to inoculation; hence, the inference is that some of it has been distributed through the body tissues. Tissue acidosis may be responsible for such distribution. The difficulty of getting blood from the ear veins in vaccine-treated animals and the marked diminution in flow of urine indicate a condition similar to that described by Brown and Loevenhart for animals receiving injections of hemin, when a pronounced fall in blood pressure and a marked dilation of the splanchnic vessels were accompanied by cessation of kidney excretion. Acute albuminuria produced by injection of uranium nitrate is not accompanied by the urinary effects which follow injections of protein; hence it is inferred that these effects are not the result of mere nephritis. From the data at hand, we have no way of determining whether or not the antibody itself is causing some of these changes.

AUTHORS' SUMMARY.

QUANTITATIVE STUDIES ON THE ACTION OF COMPOUND HEMOLYSINS. RUDOLF GAHL, NORMAN DAVID and ALICE KELLEHER, J. Immunol. **16**:209, 1929.

New experimental material is presented in graphic form. The shape of the curves which are characteristic of the hemolytic reaction, their zones and the systems which they form were discussed in a qualitative way. One of the zones was proved to be due to the presence of amboceptor in the complement. It was proposed that another zone was due to the presence of complement in the amboceptor; this would imply that heat inactivation, at least as ordinarily conducted, does not destroy all the complement contained in the amboceptor before inactiva-

tion. A third zone was considered as representing the reaction between amboceptor and complement uncontaminated by side reactions. It was shown that this zone is utilized in the Wassermann test. It was also shown that the shape of the characteristics within this zone does not vary with the specimen of amboceptor and complement serum. Cross-section curves show the typical S-shape observed by Manwaring. This shape was found to be due to the varying resistance of the individual corpuscles towards lysis. The idea advanced in the second part of this paper, that the shape of the characteristic curves depends only on amboceptor and complement serum but not on the concentration and character of the blood corpuscles, was supported by experimental evidence. AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN TUBERCULOSIS. S. A. PETROFF, ARNOLD BRANCH and F. B. JENNINGS, JR., J. Immunol. **16**:233, 1929.

From many years of study, it has become known that resistance to tuberculosis is manifested chiefly by a cellular reaction. Recent experiments have shown that the cellular reaction observed in animals sensitized with heat-killed tubercle bacilli does not differ from that seen in animals infected with living virulent organisms. Immunity produced by dead bacilli, therefore, is in no way likely to differ from that produced by living bacilli. From the studies of Bessau, Zinzzer, Ward and Jennings with guinea-pigs and from H. Langer's experiment on monkeys when he reduced the mortality in the Berlin Zoological Garden from 25 to 9 per cent after vaccination with heat-killed tubercle bacilli, and also from the observations given, it is thought that a vaccine of heat-killed tubercle can be put into practical use for the immunization of children. Good results may be anticipated. Heat-killed organisms as a vaccine are harmless for the reason that they do not propagate, while attenuated organisms entering the body may conceivably revert to their former pathogenicity.

AUTHORS' SUMMARY.

HETEROPHILE ANTIBODIES IN SERUM SICKNESS. I. DAVIDSOHN, J. Immunol. **16**:259, 1929.

The serums of twenty-one patients with horse serum sickness, whose blood was obtained during or at various intervals following the disease, were examined for agglutinins and hemolysins for sheep blood. Every one contained agglutinins for sheep blood, in titers varying from 1:4 to 1:64. Of 450 cases with no history of serum sickness, only 19 or 4.2 per cent showed agglutinins for sheep blood. All these 19 positive cases agglutinated only in the lowest dilution used (1:4). Four of the twenty-one cases showed a remarkable increase of antisheep hemolysin, complete hemolysis occurring in the following dilutions: 1:192 (= 0.0026 cc.), 1:384 (= 0.0013 cc.), 1:768 (= 0.0006 cc.), 1:1536 (= 0.00032 cc.), while the highest titer found normally in a large series of control cases was 1:128 (= 0.004 cc.). Fresh sheep erythrocytes were somewhat less agglutinable than older ones; their hemolysis was not influenced by age. Only one serum lost its antisheep agglutinins on standing. An immediate reaction in one patient following injection of horse serum is connected with the finding of agglutinins in a blood specimen obtained twenty hours following injection. The agglutinins were probably present before the injection of serum. In one of the cases of serum sickness and in one of the control cases the development of agglutinins following the injection of horse serum was observed by repeated titrations. Two patients developed agglutinins following the injection of horse serum, but no serum sickness. Three patients showed no agglutinins and no serum sickness following injection, while six patients found free from agglutinins before the injection of serum did not develop serum sickness. A patient with bovine serum sickness did not develop antisheep hemolysins. The heterophile nature of the agglutinins and hemolysins found in the serum of patients with horse serum sickness was established by experiments on absorption.

AUTHOR'S SUMMARY.

DISTRIBUTION OF ANTIBODIES IN THE SERUM AND ORGANS OF RABBITS. JULES FREUND, J. Immunol. **16**:275, 1929.

The quantity of hemolysin recoverable from the spleen, uterus or skin of actively immunized rabbits varies in relation to the hemolysin titer of the serum. These organs contain about the same amount of hemolysin per gram of tissue. The ratio between the titer of the serum and the organ extracts varies between 10:0.6 and 10:1.25. With the method employed, precipitins cannot be recovered from the organs of rabbits immunized with horse serum, crystalline egg albumin or egg white.

AUTHOR'S SUMMARY.

ON THE HETEROPHILE (FORSSMAN'S) ANTIGEN IN THE PARATYPHOID-DYSENTERY GROUP. CLAUS W. JUNGEBLUT and ALEXANDER T. ROSS, J. Immunol. **16**:369, 1929.

Immunization of rabbits with certain strains of *B. dysenteriae* Shiga or *B. paratyphosus* B was followed with great regularity by the appearance in the serum of hemolysins active for sheep and goat red corpuscles, but inactive for those of the human or rabbit. No formation of hemolysins was noted by immunizing guinea-pigs with the same cultures. Hemolytic Shiga and paratyphoid bacilli serums fixed complement specifically in the presence of true Forssman antigen. The heterophile antibodies in Shiga and paratyphoid bacillus serums were completely and specifically absorbed by contact with their homologous bacterial antigens as well as by absorption with true Forssman antigen. Intravenous injection of Shiga and paratyphoid bacillus serums into guinea-pigs was only occasionally followed by a characteristic systemic reaction due to primary antiserum toxicity. Intracutaneous injection into white guinea pigs and dogs induced frequently a well defined local, inflammatory reaction of the allergic type, particularly in the case of paratyphoid bacillus serums. Complement fixation between true Forssman antiserums and Shiga or paratyphoid B bacilli as the respective antigens was not readily demonstrable. The reactions were faint and occurred irregularly. Absorption of true Forssman antiseums by Shiga or paratyphoid B bacilli caused no definite loss of heterophile hemolysins in such serums. No evidence was found for the presence of heterophile antigen in strains of *B. paradysenteriae* (Flexner), *B. paratyphosus* A and B enteritidis (Gaertner).

AUTHORS' SUMMARY.

ANTIGENIC SUBSTANCES OF CLAUSTRIDIUM BOTULINUM. JEANNE LOMMEL and JANET B. GUNNISON, J. Immunol. **16**:403, 1929.

Substances have been obtained from *Claustridium botulinum* by extraction with 75 per cent alcohol, which contained little or no protein. They gave a positive Molisch reaction, indicating that carbohydrate was present. These substances gave strong complement fixation reactions with antibacterial immune serums. They were insoluble in salt solution and therefore failed to react in the precipitin test. They seemed to possess species specificity. The extracts had specificity neither for the serologic group nor for the toxicologic type. They apparently contained the non-specific factor responsible for the cross reactions observed among the serologic groups when intact organisms were used as antigens.

AUTHORS' SUMMARY.

LYSOZYME IN NORMAL TISSUES AND SECRETIONS. A. FLEMING, Lancet **1**:217, 1929.

Lysozyme is widely distributed throughout the body. It is found in most of the secretions and all the tissues of man, and is present in the tissues of other animals and in some vegetables. Although it may have some destructive effect on pathogenic bacteria, its extraordinary bacteriolytic effect is most easily shown on nonpathogenic bacteria, although even among these there are great differences in sensitiveness. Fleming succeeded in isolating a coccus which is remarkably sensitive to the action of lysozyme. Because it is easily dissolved he has called

this microbe *Micrococcus lysodeikticus*. When the concentration of lysozyme is great, as in tears or the white of egg, solution of this coccus is extremely rapid. The fact that lysozyme acts well on dead bacteria in an old culture is in striking contrast to the action of bacteriophage, which shows a lytic effect only on young, rapidly growing cultures. A great variety of tissues and secretions and excretions have been tested by Fleming with *M. lysodeikticus* and other organisms to see whether they contain this lytic principle. The principle was present in all the human tissues examined and in most of the secretions, except normal urine, sweat and cerebrospinal fluid. The concentration, however, varies greatly. Of all the tissues, cartilage had the strongest concentration, and an extract of cartilage corresponding to 1 part in 1,300 parts of physiologic solution of sodium chloride was capable of causing complete lysis of the test cocci in five minutes. On the other hand, the lytic action of brain tissue was weak. The great concentration of lysozyme in tears is striking. Lysozyme exists also in considerable concentration in leukocytes. The lysozyme content in the rabbit and the guinea-pig was much less than in man. The tissues of the dog stood midway between. The lysozyme concentration is greatest in the white of a hen's egg; a dilution as low as 1:60,000,000 has some lytic effect on the coccus. The yolk had no lytic action. The tissues of pike were found to contain much lysozyme, and its cartilage seemed to be quite as potent as that of man. The eggs of this fish were also found to be powerful. The tears of the rabbit, horse, sheep and turkey were all thirty or more times less potent than those of man in their action on *M. lysodeikticus*. Among the common garden vegetables tested, the turnip showed the greatest content in lysozyme, but even this was weak when compared with human tissues.

IMMUNITY IN RECURRENT FEVER. R. BRUYNOGHE and A. DUBOIS, Arch. internat. de méd. expér. **4**:441, 1929.

Recurrent fever is peculiar in that the disease consists of several febrile attacks, each lasting a few days, the attacks themselves being separated by periods of apparent health. During the fever the patient's blood abounds in spirochetes which are easily demonstrable, while in the periods of apyrexia the blood is sterile. This curious phenomenon of an alternating invasion and disappearance of the germ from the blood is interpreted as follows: During the pyrexia antibodies appear in the blood which, in a few days, reach such a concentration as to destroy the bulk of the spirochetes. A few germs escape death, however, and develop a resistance to the lysin, thus being able to multiply and eventually to lead to a new access of fever. The disease then lasts until the formed lysins definitely overpower the spirochete.

Experiments have shown that the spirochetes of each subsequent attack differ from those of the preceding. Thus, for instance, when the serum from an animal cured from his first attack is inoculated with the spirochetes which caused this attack, the micro-organism is agglutinated and dissolved; but when the same serum is infected with a spirochete from a second attack, the germ is permitted to proliferate.

Numerous workers affirm that the changes which occur in the spirochetes during the fever and the apyrexia are so profound as to create virtually new races with entirely different biologic properties. They state, moreover, that the new characteristics are fixed forever. Bruynoghe and Dubois performed a series of elaborated experiments with spirochetes of various origin coming from Germany, France, Holland, and their own country, Belgium. They reached the conclusion that the spirochetes of different attacks vary only serologically. But when inoculated into new mice the germ loses its serologic identification, becoming the "spirochete of the first attack." They further affirm that the immunity in recurrent fever is specific; that is, the animal infected with a given strain resists reinfection with the same strain only. The immunity persists for a long period and cannot be induced by vaccination with dead germs. Many strains of spirochetes causing recurrent fever are arsenoresistant.

B. M. FRIED.

SPECIFIC CELL STIMULATION. G. BESSAU and C. DETERING, Centralbl. f. Bakteriol. **106**:11, 1928.

The authors discuss the relationship of immunity of cells to antibody production and present facts tending to indicate that the stimulation of cells may lead to the formation of specific products in these cells without any connection with antibodies in the blood. For instance, in certain infections an immunity can be present long after all antibodies have disappeared from the blood. They feel that the evidence indicates that the fundamental process of immunity is a "tuning" of the cell because of its experience with the antigen; secondarily, the secretion of the cell, the antibody, appears in the blood stream.

PAUL R. CANNON.

THE MECHANISM OF "PERCUTANEOUS IMMUNIZATION" AGAINST STAPHYLOCOCCUS INFECTIONS IN RABBITS. WERNER KOLLATH and HEINRICH HERFARTH, Centralbl. f. Bakteriol. **106**:120, 1928.

The influence of Besredka's "antivirus," ordinary bouillon, certain amino-acids and heat were tested on fresh intracutaneous and subcutaneous abscesses in rabbits. The virulence of the staphylococcus culture was increased by six intra-ocular passages. Various bouillons and peptone waters as well as such amino-acids as tryptophan, tyrosine, leucine, alanine and cystine restrained the inflammatory effect, whereas heat was without effect. Bouillon previously treated with ether, after preliminary acidification and alkalization, was distinctly more protective than ordinary bouillon. Therefore, the protective effects of different bouillons depend on the lipoid content of the bouillons. This protective effect occurs only from the percutaneous injection, not from the intracutaneous. The effects were not manifested by such complete proteins as casein, depending apparently only on the peptone. The authors suggest that amino-acids in the peptone may cause the protective effect; these, however, have nothing to do with true immunity processes, but are strictly nonspecific.

PAUL R. CANNON.

Tumors

MYOMA, SARCOMA AND CARCINOMA IN THE SAME UTERUS. Q. U. NEWELL, Am. J. Obst. & Gynec. **17**:191, 1929.

The neoplasms were found in the uterus of a negress, aged 57, who complained of pain in the lower abdomen and vaginal bleeding. The tumors were all in the uterine body. An adenocarcinoma was found to make up an edematous polypoid endometrial mass; there were multiple myomas, one of which showed sarcomatous changes. This case is the fifth reported case wherein all three types of tumor were found in one uterus and the twenty-first in which carcinomatous and sarcomatous changes were found.

A. J. KOBAK.

THE INCREASED MORTALITY RATE OF CANCER. H. E. EGGERS, J. Cancer Research **12**:9, 1928.

The relative frequency of cancer as seen at present in the clinic and at necropsy as compared with old observations is beyond contest. The question arises whether the noted increase is an actual, that is, absolute, increase in the occurrence of carcinoma or only an apparent one. To answer this complicated question, Eggers reasons as follows: Cancer is only one of a number of diseases that occur most constantly at a fairly advanced age; with it, in this respect, are associated what are usually termed the "degenerative" diseases, and if cancer is becoming more frequent largely because more people are reaching a suitable age, this group of diseases should show a proportionate increase. Eggers' careful investigation, embracing a period of twenty-five years (from 1900 to 1924 inclusive), is to the effect that the mortality incidence from cancer and that from degenerative dis-

eases, respectively, show a regular and even increase. He further states that the cancer death rate and the combined death rate from the other usual diseases of advanced age show an almost strictly proportionate rate of increase for the twenty-five year period. The increase, therefore, of cancer is in all probability more apparent than real.

B. M. FRIED.

OVARIAN SECRETION AND THE INCIDENCE OF TUMOR. WILLIAM S. MURRAY, J. Cancer Research **12**:18, 1928.

Murray's material consisted of mice "the genetic constitution of the individual members of which are as homogeneous as it is possible to make them." The technic of "homologizing" the animals consisted of the mating of brothers and sisters and also of back crossing of the young animals with their fathers and mothers. Working with such a stock of animals, he attempted to investigate: (1) the effect of nonbreeding on the incidence of tumor in this strain; (2) the effect of complete gonadectomy on the incidence of tumor and on the age at which tumor appears; (3) the inhibitory influence of the testicular hormone on the appearance of tumors, and (4) the effect of complete transplantation of the ovary on the production of mammary cancer in the male. From his experiments, it appears that virginity reduces the percentage of appearance of cancer and postpones the date of the appearance of cancer for about five months; complete gonadectomy lowers the incidence in a marked degree and also probably delays the age at which tumor appears later than in either the breeding animals or the virgin females. He believes that "somthing other" than the absence of the testicular secretions is necessary before males in this line will develop neoplasms of the mammary gland. His figures also show that the ovary successfully transplanted in a castrated male behaves in a manner that is similar, if not equivalent to that of the normal ovary in a virgin female.

B. M. FRIED.

HISTOLOGIC RESEMBLANCE OF THE ROUS CHICKEN SARCOMA NO. 1 TO HODGKIN'S GRANULOMA. F. A. MCJUNKIN, J. Cancer Research **12**:47, 1928.

McJunkin's ingenious experiments with Rous' sarcoma and with material from a malignant lymphoma led him to the conclusion that (1) both round and spindle-shape cells of chicken sarcoma no. 1 are actively phagocytic for carbon in suspension; (2) both round and spindle-shape cells of the chicken sarcoma react supravitally with neutral red like blood monocytes; (3) the chicken sarcoma cells appear to be identical with monocytes, and (4) since the type cell of Hodgkin's granuloma corresponds closely with monocytic derivatives, the chicken sarcoma resembles Hodgkin's granuloma and is unlike the usual fibrosarcoma.

B. M. FRIED.

IMPLANTATION OF RAT CARCINOMA AND SARCOMA WITHIN BENIGN FIBROSARCOMA. JACOB HEIMAN, J. Cancer Research **12**:73, 1928.

Heiman inoculated rapidly growing carcinomas and sarcomas of rats into the centers of large spontaneous or transplanted fibromas or fibroadenomas of the breasts of other rats. This resulted in the growth of malignant tumors, but tumors with greatly reduced proliferative rates. In each case, the carcinoma continued to remain encysted in the center of the benign tumor, while the sarcoma seemed able to grow along the track of the needle, infiltrating the fibrous tissue and ultimately escaping into the tissues of the host. The benign tumor seemed to play a wholly neutral part, even though highly malignant cells were present in the center. This, according to Heiman, is further evidence against the hypothesis that an organism is responsible for the growth of malignant tumors, for one might expect that if such an organism were present it would stimulate the benign tumor to become malignant.

B. M. FRIED.

THE ETIOLOGY OF PRIMARY CARCINOMA OF THE LUNG. R. E. SMITH, J. Cancer Research **12**:134, 1928.

Smith investigated the specimens of primary carcinoma of the lung found at the Phipps Institute, University of Pennsylvania, with particular attention to the etiology of the tumor. He also carried on an experimental study of the same tumor in mice. For five months, respectively, two series of mice were exposed to fumes from coal tar and to fumes from the exhaust of a Ford engine, and a third series were painted with gasoline. Carcinoma of the lung did not occur in the series exposed to the fumes of coal tar; it occurred once in twenty-six (or 3.8 per cent) of the mice exposed to exhaust gas and once in twenty-nine (or 5.4 per cent) of the mice painted with gasoline. These proportions according to the author, are not greater than that of spontaneous occurrence of pulmonary cancer. The study of forty-eight cases of primary carcinoma of the lung in man did not reveal any definite etiologic factor. His observations are therefore against the suggestion that primary pulmonary cancer is caused by exposure to the fumes of coal tar or gasoline.

B. M. FRIED.

A NEW TRANSPLANTABLE RAT TUMOR. KANEMATSU SUGIURA, J. Cancer Research **12**:143, 1928.

The author describes a new type of transplantable rat sarcoma which on histologic examination resembles a small spindle cell myosarcoma. In his experiments with this tumor, he noted that there was a relationship between the growth of the tumor and the age of the host. Suckling and very young rats proved to be the most favorable soil for the continued growth of the sarcoma. In the young, regression of the tumor was present in 9.5 per cent only, whereas in the old it occurred in 87.5 per cent. However, the percentage of "takes" and their rate of growth were the same whether the hosts were young or old. He observed that rats immune to one type of tumor might or might not be immune to another kind. The transplantability of the sarcoma was completely destroyed by immersing the material in a Locke-Ringer solution or in a buffer mixture solution at p_H 2, 3 or 4 for twenty-four hours at 3 C. The capacity of the sarcoma for growth was destroyed when the sarcoma was thus treated for thirty minutes at 45 C. Dehydration completely destroyed the viability of the fresh sarcoma. The tumor-producing substance of the rat sarcoma was not filtrable.

B. M. FRIED.

ON THE FILTRABLE AGENT OF MALIGNANT TUMORS. H. E. EGGERS, J. Cancer Research **12**:222, 1928.

Investigations by Burrows and others have shown that tissue of the rat embryo of fifteen and sixteen days' development, comminuted and inserted into adult rats of the same descent after being immersed in the filtrate from the Jensen rat sarcoma, took the form of a sarcomatous growth.

Eggers attempted to determine the possible presence of, and the character of the reaction to, tumor filtrates by tissues of postembryonic origin (using for injection a tumor filtrate of sarcoma no. 10 of the Institute of Cancer Research). He studied the effect on an induced growth of connective tissue in a relatively early stage of fibroblastic development. The results obtained are to the effect that in both rats and mice the injection of a freshly prepared filtrate of the rat sarcoma was followed by an increased proliferation of already developing connective tissue. This stimulation was of temporary duration and of limited extent, and in none of the animals observed did it take the form of malignant hyperplasia. The technic used by the author is given in detail.

B. M. FRIED.

BLOOD CHOLESTEROL IN CANCER. W. L. MATTICK and K. BUCHWALD, J. Cancer Research **12**:236, 1928.

In 85 per cent of patients with cancer somewhere in the body and likewise in cancerous mice, the cholesterol in the plasma was found higher than that in

the whole blood. But in noncancerous persons and in healthy mice, the plasma cholesterol was found lower than that in the whole blood. In view of the fact that similar studies were not performed on persons with diseases other than cancer, no definite conclusion can as yet be drawn from these observations.

B. M. FRIED.

THE GLYCOLYTIC ACTION OF SOME TUMORS AND THE EFFECT OF INSULIN. S. L. BAKER, F. DICKENS and E. J. GALLIMORE, Brit. J. Exper. Path. **10**:19, 1929.

A marked difference is found between the anaerobic metabolism of dextrose in normal tissues and that in malignant tumors, the latter producing from five to ten times as much lactic acid as the former. The addition of insulin or thyroxin has no demonstrable effect.

PEARL ZEEK.

INTRA-EPITHELIOMATOUS HYPERGENESIS OF ELASTIC TISSUE. R. ARGAUD and J. DUCUING, Ann. d'anat. path. **6**:37, 1929.

In a cancer treated with the x-rays, the authors discovered an abundance of elastic tissue. A detailed investigation of the tumor led them to the conclusion that the epitheliomatous cell possesses the property of forming elastic tissue. It is possible, they say, that the elastic hyperplasia described in the vicinity of cancerous nodules of the breast is of epithelial origin.

B. M. FRIED.

A STUDY OF THE LIPOIDS OF RATS, CARRIERS OF ADENOCARCINOMA. ADA BOLAFFI, Tumori **3**:1, 1929.

In the bodies of rats, with the development of adenocarcinoma a remarkable impoverishment of phospholipins of the fraction soluble in ether and precipitated by acetone takes place. It is reduced to about one third of the amount found in normal rats. The tumors contain lipoids of this group in a proportion equal to or a little less than the average in the normal tissues. For this reason, the reduction of these lipoids in the tissues of the rats with tumors is apparently not due to a concentration of them in the tumors, but to a partial destruction of them in the bodies of the rats. The latter might be caused by an alteration of the lipoid metabolism. In the tumors there is a certain concentration of lipoidal phosphorus, which may be due to the presence of unknown phosphatids that are rare or missing in the normal tissues. In other lipoid fractions there is no appreciable difference.

W. OPHÜLS.

ON CERTAIN RESEMBLANCES BETWEEN THE TUMORS OF VEGETABLES AND THOSE OF ANIMALS. EUGENIO CENTANNI, Tumori **3**:17, 1929.

The tumors of animals and the tumors of vegetables resemble each other in their power of spontaneous development after they have been started by irritative agents. Extracts of the tumors of plants, do not stimulate the growth of the tumors of animals. This fact tends to show that the two differ considerably in their biologic activity.

W. OPHÜLS.

CARCINOMATOUS TRANSFORMATION OF ULCER OF THE STOMACH. E. KLEIN and F. DEMUTH, Beitr. z. path. Anat. u. z. allg. Path. **79**:117, 1928.

The authors discuss first the clinical and histologic criteria on which may be based a decision as to the transformation of ulcer of the stomach into carcinoma. How differently these criteria may be interpreted by different observers is attested by the fact that Konejyzky reported carcinomatous transformation as occurring in 3 per cent of ulcers, Hauser in 6 per cent of ulcers and in 7 per cent of scars of ulcers, whereas Wilson and MacCarty reported it as occurring in 71 per cent.

The work of the authors was concerned, not with the study of a large series of gastric ulcers to determine how many might show carcinomatous changes, but with the careful study of a small series of ulcers some of which showed carcinoma and some not, with the aim of determining whether any changes other than those easily recognized as carcinomatous might be considered characteristic of carcinoma. Moszkowitz had described groups of deeply staining epithelial cells as histologically pathognomonic of carcinoma. Klein and Demuth do not believe that the histologic diagnosis of carcinoma can be based on such cells nor on single cells, no matter how atypical or heterotopic. They lay greatest stress on the relatively greater formation of scar tissue in the submucosa at the margin or base of the ulcer when the latter becomes carcinomatous than when it remains benign.

O. T. SCHULTZ.

CHROMAFFIN TUMOR OF ZUCKERKANDL'S ORGAN. ERNA HANDSCHIN, Beitr. z. path. Anat. u. z. allg. Path. **79**:728, 1928.

A tumor of Zuckerkandl's organ, which the author had the opportunity to study, led to a histologic investigation of this paraganglionic tissue to determine the time of disappearance of its chromaffin tissue and whether it might persist late enough in life to account for tumors encountered in adult life. Regression of the chromaffin tissue begins at the end of the first year of life and continues fairly actively until puberty. Some chromaffin cells, however, were found in a person aged 26. No ganglion cells were seen at any age period. The tumor studied occurred in a man aged 45 and was a chance observation at necropsy, the patient having died after resection of the stomach for carcinoma. Blood pressure had been normal and there had been no clinical symptoms that might be ascribed to the tumor. The latter measured 3.5 cm. in its greatest dimension. Its cut surface was pale and somewhat translucent. Microscopically, it was moderately cellular, but did not give the impression of active growth. The tissue did not give the chromaffin reaction, but an extract made from a portion of the fresh tissue had the characteristic effect of epinephrine on the pupil of the excised eye of a frog. The tumor is believed to have arisen from persisting chromaffin cells. Because chromaffin tissue occurs in what have been called glands of internal secretion, the author makes the unfortunate suggestion that the tumor described by her is an adenoma.

EPITHELIOMA (SQUAMOUS CELL CARCINOMA) OF THYROID. M. KARTAGENER, Beitr. z. path. Anat. u. z. allg. Path. **79**:843, 1928.

The author describes a squamous cell carcinoma of the left lobe of the thyroid of a man, aged 64. There was no hornification. The esophagus and trachea were invaded, but the author does not think that the tumor originated in either of these structures, but in the thyroid itself. The reason for the reporting of the tumor lies in the fact that it contained also perithelioma-like areas. These consisted of large cylindric cells the bases of which lay directly on the endothelium of a capillary network. The cells were epithelial in type. The author considers this element in the tumor not a true perithelioma but a carcinoma derived from the glandular epithelium of the thyroid. He discusses the possible origin of the squamous cell portion by metaplasia or from misplaced squamous epithelium, but comes to no decision.

O. T. SCHULTZ.

CHLOROMYELOSIS WITH AN UNUSUAL EOSINOPHILIA. G. SEEMANN and A. SAJZEWA, Folia Haemet. **37**:258, 1928.

The patient, a man aged 42, showed a temperature of 38 C., a slight swelling of the cervical lymph nodes and some recent loss of weight. He complained of weakness and generalized pain. The blood picture, except for an eosinophil count of 49 per cent, was negative. The necropsy revealed chloromas that were confined to the periosteum. The high eosinophil count noted for smears was also found for the tissues. The authors designate the disease as chloromyelosis, including it in the group of leukemias.

B. M. FRIED.

OVARIAN ADENOMA. O. HEESCH, Virchows Arch. f. path. Anat. **268**:280, 1928.

The author concludes that adenoma tubulare ovarii of Pick is identical with the tubular adenoma of the atrophic testicle; also that other forms of tubular ovarian adenoma may occur which in their morphologic details closely resemble that of the testicle, but the true identity of which is not entirely clear.

V. C. JACOBSEN.

Medicolegal Pathology

OCCUPATIONAL POISONING IN MANUFACTURE OF LUMINOUS WATCH DIALS. HARRISON S. MARTLAND, J. A. M. A. **92**:466, 1929.

Five of fifteen deaths known to have occurred among 800 girls employed in painting watch dials with luminous paints were proved to be due to radium poisoning. The exact number who have died of or who have been harmed by this disease is unknown. Various factors are involved in the production of this occupational poisoning other than the pointing of the paint brushes with the lips. The luminescence was produced by scintillation. Radon, radium, mesothorium or radiothorium was mixed with zinc sulphide and salts of rare earths; from 0.7 to 4 mg. of radium element was present in 100 Gm. of zinc sulphide; from 15 to 215 micrograms of radioactive substance was the theoretical amount ingested each week. From 14 to 48.282 micrograms was found in entire skeletons. The so-called lethal dose, estimated as radium element, ranges from 10 to 180 micrograms.

Necrosis of the jaw, leukopenic anemia, severe buccal lesions and terminal sepsis were present in the fatal cases. Symptoms were first noted from one to seven years after the patients ceased working as dial painters. Chronic radiation osteitis and subsequent bone lesions are present in patients still living. During life the diagnosis may be made by the demonstration of either emanations by means of an electrometer or alpha particles (from expired air), by scintillation methods. After death the diagnosis may be based on the radioactivity as determined in the bones by photography and in the soft tissues by the alpha or gamma electroscope.

The author interprets the disease as follows: After ingestion of the radioactive substance it is deposited in the form of an insoluble sulphate in the phagocytic cells of the sinusoids of the reticulo-endothelial system, especially in the bones, liver and spleen. In the bones the juxtaposition of the blood forming centers and the affected cells of the sinusoids, whence the destructive alpha rays emanate, produces the characteristic blood changes.

The preponderance of mesothorium is of toxicologic importance; it can produce in exposed persons aplastic anemia, myelogenous or lymphatic leukemia, sarcoma, sterility, radiation osteitis, necrosis of the bone and hemorrhagic diathesis, and endocarditis, sepsis or septic bronchopneumonia may be superimposed.

The hemorrhagic diathesis may be produced by a diminution of the blood platelets, either by direct effect of the alpha particles on the megakarocytes or secondary to the sepsis. The blood picture shows a color index above unity; anisocytosis with macrocytes and megaloblasts; icterus index normal or below; negative van den Bergh reactions. "At autopsy there was no pronounced increase in hemosiderin deposits in the liver, spleen and kidneys, such as is seen in addisonian anemia." The bone-marrow of the femors was dark red (hyperplastic) in all cases examined.

Radium-mesothorium necrosis is now one of only ten occupational diseases which come under the compensation laws in New Jersey. In 1926 the families of two girls dying from radium-mesothorium necrosis received compensation. In the case of the five girls said to be suffering with the disease, an uninvolved judge arranged for a settlement out of court. No legal responsibility was assumed by the company.

E. L. BENJAMIN

RUPTURE OF ESOPHAGUS BY INDIRECT VIOLENCE. J. R. MURDOCK, Lancet **2**: 1292, 1928.

A boy, aged 6 years, was run over by a motorcycle and died a few hours later. There were fractures of the left humerus and of the left side of the base of the skull; and also a longitudinal tear, 1¼ inches long, in the esophagus ¾ inch above the diaphragm which was torn slightly at the esophageal opening.

ASTONISHING REVELATIONS AT POSTMORTEM EXAMINATIONS. R. KOCKEL, Arch. f. Kriminol. **83**:242, 1928.

An extensive comminution of the cranial bones and injuries of the brain were found in the body of a man lying dead so far from where an explosion occurred that it was thought he had died from heart disease. A similar mistake was made in giving heart disease as the cause for death of a man found on a railroad track and a woman found on the street. Postmortem examination disclosed extensive crushing injuries in each body. Two other deaths supposed to have occurred from heart disease turned out to be due to bolus asphyxias.

Exhumation and examination of the body of a man pensioned for many years for an alleged heart disease following injury of the chest, not only failed to reveal any justification for the pension, but demonstrated that death was caused by a phlegmonous inflammation of the face. The attending physician had attributed death to the injury years before, and on that basis it was planned to have the pension continue to the family. Three deaths from electrocution are reported, but the exact manner of death was not learned until careful inquiry was made of the circumstances, an absence of disease and injury in the bodies established, and further examination had revealed small external wounds made by the current. Carbon monoxide was suspected as the cause for one of these deaths, and it was said that a second of the three persons electrocuted had suffered from heart disease for a long time. The attending physician had certified that as the cause of death.

A young married couple fought, and the husband killed his wife with a hatchet. He then set fire to the body with petroleum in the kitchen and went away. He confessed when told of the absence of soot in the lungs and of carbon monoxide in the blood, of the postmortem character of the burns and that a microscopic examination had demonstrated feathers in the burned clothing. The feathers were from a pillow that had become blood-stained. In the body of a man pensioned since the war for pulmonary tuberculosis and some nervous disease, these were found absent; death was caused by influenza. Two other deaths from hydrofluoric acid are reported; both were criminal poisonings of women by a man which were unexpectedly encountered. Death supposedly due to a street accident turned out to be from pernicious anemia and spontaneous hemorrhages; ruptured liver with huge hemoperitoneum was found in another body when it was supposed that injuries of the head had caused death.

It is difficult to accept the conclusions given by Kockel for the remaining one of the sixteen deaths, each with surprising revelations, with which his article is concerned. It has to do with a street fight and stab wounds of one of the combatants, the removal of 1 liter of blood from his chest two days after the fight and death with a fever four days after the thoracentesis. At the postmortem examination it was decided that none of the stab wounds, some of which were in the thorax on the side tapped, were mortal and that the fluid removed during life was in reality the bloody exudate of a pleuritis present at the time of the fight. Pleurisy was given as the cause of death. This account should include a description of what was done, if anything, to ascertain their depth and also whether any healing had taken place in any of the wounds of the chest during the six days the man lived.

E. R. LE COUNT.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 14, 1929

J. HAROLD AUSTIN, M.D., *President*

A CASE OF SEPTICEMIA IN MAN DUE TO BACILLUS SUIPESTIFER. JOHN T. BAUER and MARGARET MCCLINTOCK (by invitation).

Organisms of the paratyphoid group other than *B. paratyphosus* A and B can give rise to febrile conditions in man, simulating typhoid fever. The following case illustrates the importance of further studies in instances in which the Widal test is negative for *B. typhosus* and *B. paratyphosus* A and B, and organisms isolated from the patient fail to react with the usual diagnostic typhoid and paratyphoid serums.

An Italian stone mason, aged 46, was admitted to the medical service of Dr. Norris at the Pennsylvania Hospital in August, 1927, with symptoms of headache, weakness and fever. Although no rose spots were seen, the clinical manifestations of a temperature of 103.8 F., a pulse rate of 92 beats per minute, a palpable spleen and liver and a leukopenia of 6,000 cells strongly suggested typhoid fever. The condition failed to improve, and death occurred on the twenty-first day of the disease. Permission for necropsy was not obtained. The source of infection was unknown, but the drinking water was suspected.

Three blood cultures were taken, and all yielded organisms which culturally proved to belong to the hog-cholera group. Two Widal tests were negative for *B. typhosus* and *B. paratyphosus* A and B, yet they showed strong agglutination in a dilution of 1:10,000 for *B. suipestifer* and the organisms isolated from the blood of the patient. By means of reciprocal agglutinin absorption tests, the close relationship of this organism to *B. suipestifer* was confirmed.

This article will be published in full in the *Journal of Infectious Diseases.*

SIMPLIFIED METHOD OF INJECTING THE CORONARY CIRCULATION. JOHN EIMAN and ETHEL L. RAHE.

Numerous methods have been employed for the demonstration and study of the circulation of the heart. They include dissection and injection with metals of low melting point and other substances, followed by corrosion. Later stereoscopic roentgenograms and clearing methods were introduced. Some of these methods were employed for special problems, such as the study of anastomoses, variations in the branches and distribution of the branches of the main vessels. Dr. Merritt B. Whitten (*Arch. Int. Med.* **42**:846 [Dec.] 1928), published an exhaustive review of the literature on methods of study of the circulation of the heart.

The method we are describing is not new. In 1896, Hermann Braus was apparently the first to inject the coronary arteries with a metal and to study stereoscopic roentgenograms (*Anat. Anz.* **11**:625, 1896). Oberhelman and LeCount (J. A. M. A. **82**:1321 [April 26] 1924), employed the foregoing method, using mercury.

Our technic of injection is as follows: Hearts are removed without injuring the musculature and with fairly long portions of the large vessels remaining. Clots are removed from cavities of the heart, and the blood is washed out with running water. The heart is placed on an aluminum tray covered with a towel. The aorta is slit on the anterior surface almost down to its origin. Cannulas are inserted into the coronary arteries. A heavy ligature is passed around each cor-

onary artery, as close to its origin as possible, by means of an aneurysm needle. Ligatures are tied firmly but not too tightly, and the cannulas are withdrawn until their flanges rest against the ligature.

Purse-string sutures are placed loosely around the orifice of the inferior vena cava and the largest of the pulmonary veins entering the left auricle. In order to distend slightly the cavities of the heart, two pieces of Esmarck rubber tubing should be introduced into them, which measure approximately 20 by 4 cm., one end of which has been made airtight and the other end attached to rubber pressure tubing. The tubing from the Esmarck drains is connected to a metal "Y" to the single end of which is attached by means of rubber tubing, an ordinary blood pressure bulb. One should tighten the purse-string ligatures in order to keep the Esmarck tubing in place, and should inflate the same and clamp the rubber tubing. Care must be taken not to overdistend the cavities, as this would interfere with the injection of the vessels. Mercury is placed in a separatory funnel which is attached to an upright stand by means of a clamp. Rubber tubing is attached to the funnel, and in its free end an adapter is fastened securely, which fits the cannula. The mercury level is adjusted to about 150 cm. above the midplane of the heart, all the air is expelled from the tubing and the tubing is clamped securely. The stop-cocks of both cannulas should be open. The adapter should be inserted into the cannula opening into the left coronary artery. The mercury is slowly released and permitted to flow into the arteries. If there is any escape of mercury from the smaller vessels, these should be clamped and tied off. Within from forty-five to one hundred and twenty seconds, mercury appears at the mouth of the cannula inserted into the right coronary artery. The stop-cock of the cannula in the right coronary artery should be turned off, and four or five seconds later that of the left. The tubing from the reservoir of mercury should be clamped and disconnected. The tip of the heart is elevated by means of the towel on which it is lying so as to remove any loose mercury that has escaped into the chambers of the heart. Stereoscopic roentgenograms are then made of the heart.

The cavities of the heart should be opened as soon as possible, and examined and described. Sections are taken for microscopic study.

Sometimes there is considerable escape of mercury through the thebesian veins. We have not succeeded in forcing mercury over into the veins of the heart even with a pressure up to 500 mm.

By this method it is impossible to inject the capillaries, precapillaries or even slightly larger vessels. It gives, however, excellent pictures of the gross circulation of the heart and enables one to visualize the coronary circulation in its entirety. This method supplies data that enable one to interpret more accurately gross and microscopic observations and to correlate them with the clinical picture of the case. Oberhelman and LeCount, on injecting twenty-six hearts, found that in nine both coronaries could not be injected by forcing mercury into the orifice of one coronary. In sixty adult hearts into which injections were made, we experienced such difficulty in only two cases, one case of occlusion of the orifice of the right coronary, the other of embolism in the left coronary. In cases of thrombosis and embolism, if the occlusion of the coronary occurs about 1 cm. or more from the orifice, the portion of the coronary proximal to the occlusion is filled through anastomosing branches. In cases of gradual occlusion of the main trunks of the coronary arteries or their larger branches, compensatory enlargement of anastomosing branches can be demonstrated in some instances.

Spalteholtz (Die Arterien der Herzwand, 1924), Gross (Blood Supply of the Heart, 1921) and others have shown that near the surface of the heart of the new-born infant anastomosing arterioles exist between the right and the left coronaries. They were not able to demonstrate any anastomosis in the interventricular septum. When injections were made into hearts of new-born infants and children of 2½ years, we could not force mercury from the left coronary into the branches of the right. In a child, aged 5 years, both coronaries were completely injected through the orifice of the left. This suggests that anastomoses between larger vessels do not exist at birth, but that they develop some time between the ages of 2½ and

5 years. There is a rather strikingly different appearance between the branches and the distribution of the coronaries of children and young adults, on the one hand, and older adults on the other. In children the branches are fewer, coarser and of rather uneven distribution. In young adults, the anastomoses between the left and the right coronaries are maintained through one, two or three larger branches. We have been designating the latter type of arterial tree as juvenile. Occasionally, we have seen the juvenile type of anastomosis in older adults. It is rather difficult to interpret what this means. Would it not be possible that in cases in which the main anastomoses are maintained through one or two larger branches, the patient would die rather suddenly if one of those branches should become occluded? It is more than probable that in cases of thrombosis or embolism the question of patients surviving or dying depends on the efficiency of anastomoses between the right and the left coronaries. Nusbaum (*Arch. f. mikr. Anat.* **80**:450, 1912) and Gross have reached the conclusion that capillary and precapillary anastomoses were inadequate to maintain sufficient collateral circulation in emergencies but may become adequate with gradual occlusion.

Changes in the lumina of the larger vessels due to arteriosclerosis are readily demonstrated. The outline of the vessels is irregular; disproportionate narrowing at bifurcations or origins of branches are seen. Sometimes calcareous infiltration of the walls is apparent. Although the changes are most striking in the larger vessels, damage or changes in the myocardium are seen around the capillaries and arterioles. In cases of sclerosis of the coronaries, diminution in the numbers of capillaries, compression and obliteration are seen. There are retrograde changes in the muscle cells around these capillaries and replacement of degenerated muscle cells by connective tissue. As the sclerosis of the larger vessels becomes more marked, the degeneration of muscle and the proliferation of connective tissues likewise become more extensive.

If possible, the injection of the arteries should be done in all cases that come to autopsy, but particularly in cases with a history of heart disease. The information gained by this simple method is of great value and offers many possibilities for the study of the coronary circulation in general.

It enables one to determine: (1) the location and extent of thrombosis; (2) the location of the emboli; (3) the degree and extent of sclerosis of the arteries, and (4) the rôle of the coronary vessels in their relation to myosclerosis.

A Theoretical Consideration of the Interrelation of Certain Immune Reactions Concerned in the Production of Chronic Disease. James C. Small.

The hypothesis was suggested that certain of the manifestations of chronic disease depend largely on an abnormal state of a person, rather than on any unusual pathogenicity of the bacteria concerned in its etiology. The hypersensitive or allergic state of a person to a bacterial antigen was discussed and an attempt to explain the manner in which such a state may act continuously in producing chronic disease was presented in the light of the knowledge of such states induced in experimental animals.

The guinea-pig into which injections of horse serum are made was chosen as an example. From the time the animal receives a single injection onward, it can not longer be considered in a normal state. At the end of a period of days, it becomes so abnormal that a hundred-thousandth or a millionth part of the original injection of horse serum will produce rapid death. There has been no change in the inherent nature of the horse serum by virtue of which it can be regarded as any different chemically from the relatively inert substance it was for the animal primarily. The changed conditions, therefore, must be sought in the animal, which has become hypersensitive to the horse serum. Under proper conditions of the experiment, this hypersensitive condition may be maintained for indefinite periods. As long as the animal is in this condition, injections of small amounts of horse serum are likely to produce a fatal result, and injections of extremely minute amounts will produce tissue damage without an immediate fatal result.

One has, therefore, the conditions necessary for producing pathologic lesions over an extended period by the exhibition in minute amounts of a substance not primarily harmful to the animal. In this conception, then, there is a logical basis for the continued low-grade activity of chronic lesions in man. An insignificant focus of infection with streptococci, for example, may conceivably hypersensitize a person to some of the products of the bacteria. The constant supply of this antigenic substance from the focus continues to furnish the irritant responsible for widespread chronic degenerative lesions. This conception eliminates the necessity of attributing a primary highly pathogenic property to the streptococcus, since it, as the horse serum, may have in its primary contact with the animal organism feeble irritating properties.

This conception raises a fundamental question in treatment. After diligent search for, and careful elimination of, the foci of low-grade infection which presumably chiefly maintain the allergic state, is the problem in specific therapy that of immunizing or that of desensitizing the patient? There is suggestive evidence from the experimental standpoint that the hypersensitive state may be an indication of the beginning of the immunity. If the immune state can be raised to such a height that hypersensitive phenomena are no longer present, this procedure obviously promises the more permanent benefit. When this is not possible, the method of desensitization is available and offers the advantage of more prompt responses which, however, may not be permanent unless the principal sensitizing foci of infection have been eliminated.

SPONTANEOUS TUBERCULOSIS IN SNAKES. JOSEPH D. ARONSON.

Four garter snakes (*Thamnophis sirtalis*), which died at the Philadelphia Zoological Garden, showed the following lesions at necropsy: The livers of all of them were studded throughout with miliary tubercles. In one, a cavity containing mucopurulent material was found in the connective tissue above the upper pole of the liver. The right lung of three of the snakes contained areas of consolidation, and the peritracheal lymph nodes were swollen. In two specimens the spleen was swollen, soft and a uniform gray.

Histologically, the lesions from the various organs were found to be similar and to consist of a diffuse-staining center surrounded by layers of large cells with clear vesicular nuclei. A layer of dense connective tissue separated the lesions from the adjacent tissue, and numerous deeply staining cells and eosinophils were found throughout the section. The pulmonary alveoli contained numerous desquamated cells and numerous eosinophilic cells. No calcification or giant cells were noted. A small number of extracellular, beaded, acid-fast bacilli, as well as a large number of nonacid-fast bacilli having the same morphology, were scattered throughout the tubercle.

In the smears prepared from the various organs, from the cavity above the liver and from the cultures, an acid-fast pleomorphic bacillus was noted. Numerous beaded and barred forms were also found.

The bacilli stain readily with carbolfuschin and retain the stain when exposed to 25 per cent sulphuric acid for ten minutes, but many of them are decolorized by a three-minute exposure to hydrochloric acid, 5 per cent nitric acid or 10 per cent sodium sulphite. When exposed for three minutes or longer to 95 per cent ethyl alcohol, the organism is completely decolorized; it is gram-positive.

The bacillus grows readily at 25 C. on Dorsett's medium, Petroff's medium and on glycerin-agar. The colonies are elevated, moist and pink, later becoming salmon color.

The cultures were found to be pathogenic for goldfish, frogs, snakes, chameleons and lizards, but nonpathogenic for rabbits, guinea-pigs and chickens.

By means of the agglutination test and of absorption experiments, it was found that cultures isolated from the various snakes were antigenically the same and that they differed from *M. marinum, M. chelonei, M. ranae* and from the acid-fast bacillus isolated by L. Rabinowitch-Kempner from boa-constrictors.

The organism isolated from these snakes is considered a new species, for which the name *Mycobacterium thamnopheos* is proposed.

RATE OF ABSORPTION OF HORSE SERUM AFTER INJECTION AND ITS RELATIONSHIP TO SERUM DESENSITIZATION AND SERUM THERAPY. LOUIS TUFT.

By means of the precipitation test, with the use of antihorse immune rabbit serum to provide the antibodies, it was possible to detect the presence of horse serum in the circulation after subcutaneous or intramuscular injection, and in this way to determine that after either method of injection in the three patients studied horse serum is slowly absorbed from the tissues, the major portion being absorbed in from fifteen to twenty-four hours. The amount of horse serum in the circulation then remains practically stationary for three or four days; then it slowly decreases in amount until at the end of seventeen days only a trace can be detected. In one case, study of the urine for horse serum after injection proved negative; evidently, this serum is not filtered out as such by the urine. The slow rate of absorption of horse serum offers a possible explanation of the failure of the usual methods of desensitization to protect against fatalities in the reported cases. It is therefore suggested that the methods of desensitization now in use be modified so as to allow a period of at least from fifteen to twenty-four hours, during which time enough of the horse serum may be absorbed to bring about desensitization. The method suggested consists of an injection of 0.1 cc. intramuscularly, followed in one-half hour by 0.3 cc., after an hour by 0.5 and after two hours by 1 cc. If no reaction occurs after a subsequent lapse of two hours, then the remainder of the serum can be given in divided doses every three hours over a period of twenty-four hours. If intravenous administration is paramount, it should be preceded by intramuscular injections over a preceding period of twenty-four hours and then intravenous injections of increasing doses every hour, any sign of untoward reaction being watched for carefully.

Preceding any form of serum therapy and irrespective of the method, a skin test with horse serum should be done. If the reaction is negative, the serum may be given with safety. If positive, it may indicate the presence of either a natural form of hypersensitiveness or an acquired or induced form. The studies and experiences mentioned suggest that serum desensitization in the human being should be limited only to patients with an acquired or induced form of hypersensitiveness to horse serum and should not be attempted in the natural or atopic form, in which it is not only ineffective but may be dangerous. Too much reliance should not be placed on any method of desensitization in the human being, the efficacy being at best doubtful. Finally, a slow absorption rate for horse serum suggests a similar state for immune antibodies; hence, intravenous administration is always preferable for a rapid clinical effect, unless contraindications exist.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, March 11, 1929

ESMOND R. LONG,
President, in the Chair

ON THE OCCURRENCE OF TRUE MIXED CARCINOMATOUS AND SARCOMATOUS TUMORS (SARCOCARCINOMA) WITH REPORT OF A MIXED CARCINO-CHONDROSARCOMA OF THE THYROID OF A DOG. ROBERT MASON AND H. GIDEON WELLS.

The infrequency with which malignant tumors present histologic features indicating that they are composed of both carcinomatous and sarcomatous elements is so striking that at times the existence of true mixed sarcoma and carcinoma has been questioned. As bearing evidence on the disputed question as to the genuineness of mixed sarcocarcinomas there was reported a case of a large mixed tumor arising in the thyroid of a dog. The tumor consisted of a mixture of adenocarcinoma with osteoid sarcoma. There were many metastases in the lungs, some

consisting solely of carcinoma, some solely of osteoid sarcoma and some presenting a mixture of both elements. Carcinoma cells could scarcely simulate such cartilaginous and osteoid structures, and hence there can be little room for doubting that these are truly sarcomatous portions of a mixed tumor. The occurrence of metastases showing only carcinomatous elements, and metastases of pure sarcomatous character, supports further the assumption that in the primary tumor there were both carcinoma cells and sarcoma cells, which when transplanted separately as metastases continued to exhibit and demonstrate their individual characaters. (The full report will be published in the *Journal of Cancer Research.)*

SARCOMA OF THE STOMACH. GEORGE M. CURTIS AND P. A. DELANEY.

Primary sarcoma of the stomach is rare, although more than 250 cases have been reported. It occurs once in 2,260 necropsies (Hosch: *Deutsche Ztschr. f. Chir.* **90**:98, 1907) and constitutes between 1 and 2 per cent of the malignant growths of the stomach. Even higher incidences are reported (Fenwick: *Lancet* **1**:463, 1901). Smithies, however, found but 4 cases in "a study of 921 operatively and pathologically demonstrated instances of gastric cancer" (Cancer of the Stomach, Philadelphia, W. B. Saunders Company, 1916). Unlike carcinoma, it affects the sexes equally (Hesse: *Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.* **15**:550, 1912). On the average, the onset is between the ages of 44 and 45, and the greatest frequency is between 40 and 60. The youngest patient, a child aged 3½, had a spindle cell sarcoma (Finlayson: *Brit. M. J.* **2**:1535, 1899). The first authentic case was reported by Virchow: a round cell endogastric sarcoma of the pyloric region in "ein junges Mädchen" (Die krankhaften Geschwülste, ed. 2, Berlin, 1864). Recently, several sporadic cases have been reported; for example, Brander's (*Brit. M. J.* **1**:139, 1927), which was soon followed by three others (*Brit. M. J.* **1**:393, 632 and 845, 1928). Without doubt, a large number of similar cases remain unreported. It is also probable that on careful microscopic study several cases among those thought to be carcinoma will prove to be sarcoma. The most recent case I have found is that of Pemberton, an exogastric fibrosarcoma of the pyloric region (*Proc. Staff Meetings Mayo Clinic* **4**:17, [Jan. 16], 1929).

The etiology and histogenesis of this disease are obscure. Gastric ulcers have been unnecessarily accused, likewise trauma. There is evidence however, of sarcomatous degeneration of benign gastric myomas, as in von Eiselsberg's case as studied by Nauwerck (*Arch. f. Chir.* **54**:568, 1897). Other similar cases are reported (Konjetzny: *Ergebn. d. Chir. u. Orthop.* **14**:256, 1921). Sarcoma originates most frequently in the submucosa, less frequently in the muscularis and rarely in the mucosa or subserosa (Hesse).

Grossly, three forms are described (Konjetzny). The exogastric protrudes from the wall of the stomach in varying degrees; stalked, broad-based and intermediate forms are described. The intramural forms are usually infiltrating. The endogastric forms are more commonly fungous and ulcerating. Multiple forms are described.

The greater curvature, posterior wall, pylorus and lesser curvature are the common locations involved, in descending order of frequency. The ostia of the stomach are rarely involved (Lofaro: *Arch. gén. de chir.* **4**:8, 1909). This is of clinical importance in connection with the infrequency of obstruction resulting from these neoplasms.

Hesse carefully analyzed the microscopic character of 144 cases. The round cell forms predominate, particularly lymphosarcoma. It is often difficult to differentiate these forms from one another and from regional lymphocytic tumors. There follow in order spindle cell sarcoma, myosarcoma, mixed fibrous and muscular forms, mixed cell sarcoma and then rarer varieties, such as angiosarcoma.

Metastases are not so frequent as with carcinoma, occurring in about 37.5 per cent of the cases, and are usually of the lymph nodes or liver (Aschoff: *Path. Anat.* **2**:735, 1923). Myosarcoma may form enormous cystic metastases in the liver. In Hosch's case, the liver weighed 10,900 Gm. and contained many

large cysts. Secondary sarcoma of the stomach is considerably more rare than the primary form (Ziesché: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **20**:377, 1909).

Malignancy of the stomach is not always accompanied by even moderate symptoms of gastric disease. This applies particularly to certain cases of extrinsic sarcoma, as in the case reported. In this case there were practically no gastro-intestinal symptoms during the disease; there was, however, a marked secondary anemia, and in the investigation of its cause the tumor was discovered at fluoroscopy. Resection of a leiomyosarcoma of the pyloric region was followed by recovery and a restitution of the blood.

A housewife, aged 59, came to the surgical clinic on June 11, 1928, because of pain in the right wrist, subsequent to a Colles' fracture sustained three months previously. At that time there were no abdominal symptoms. Her appetite was good, the bowel movements were regular and so far as she knew the stools were normal. There was no abdominal distress or flatulence. There was no history of cancer in the immediate family; however, there was severe tuberculosis. During the preceding four months, the patient had lost about 15 pounds (6.8 Kg.). Results of examination of the chest and films of the chest were essentially negative, although there was a history of an old asthmatic bronchitis. The urine was normal, and the blood pressure was 150 systolic and 90 diastolic.

Owing to some dyspnea and palpitation which had become worse during the previous two months, until it was noted even on slight exertion, she was referred to the cardiac clinic for further study. There a severe anemia was disclosed, with 8.6 Gm. of hemoglobin per hundred cubic centimeter of blood and 3,320,000 erythrocytes. The leukocyte count was 6,600, with a slight lymphocytosis and evident but moderate poikilocytosis. The cause of the anemia was obscure.

During the ensuing month the patient became weaker, lost more weight and was finally forced to remain in bed. Vague symptoms such as heart-burn and mild epigastric distress appeared, and her appetite diminished. The anemia increased, and there was marked poikilocytosis, anisocytosis and achromia. The lymphocytosis persisted as the leukocyte count became 10,800. Then rather suddenly a severe diarrhea began with nausea and vomiting. The latter may have been due to medication. She became so exhausted that it was necessary to take her into the hospital on a stretcher.

Again a severe secondary anemia was found, the cell count revealing: red blood cells, 2,000,000; white blood cells, 9,600; neutrophils, 68 per cent; lymphocytes, 26 per cent; reticulocytes, 6.6 per cent, monocytes, 4 per cent, basophils, 1 per cent, and eosinophils, 1 per cent. There was a definite variation in the size and shape of the erythrocytes, and in their staining qualities. The hematocrit reading was 22. The oxygen capacity of the blood was 7.6 per cent by volume. Both qualitative and quantitative van den Bergh tests were negative. The fragility test was normal. An Ewald meal revealed 10 degrees of free acid, and blood was found in both the gastric content and the stools. This led to fluoroscopy in an endeavor to determine the source of the blood loss. Rather surprisingly a large filling defect of the lesser curvature at the pylorus was found, with a palpable mass and considerable rigidity of the adjacent wall of the stomach. The peristaltic waves did not pass through this area, and yet the stomach emptied rapidly and completely. Films clearly revealed the defect and suggested a fungating neoplasm of the lesser curvature, above the pylorus, without obstruction.

Owing to the motility of the stomach and the absence of demonstrable metastases, particularly in the roentgenograms of the chest, it was thought that the neoplasm was probably resectable, and operation was advised. The patient was given two preoperative blood transfusions, 500 cc. of citrated blood, type IV, being used. The second was followed by a rather severe reaction. On July 26 the abdomen was opened, and a resectable tumor was discovered at the pylorus. The tumor was ovoid, about 4 inches (10.16 cm.) in length, and was attached by a broad base to the anterior wall just below the lesser curvature. The omentum was firmly attached to its anterior surface, and the region of attachment

was hemorrhagic. No metastases were found. Resection was followed by a retrocolic Reichel-Polya gastro-enterostomy without an entero-enterostomy between the afferent and efferent loops.

Recovery was complicated by rather severe vomiting for about a week. This was controlled by continuous gastric aspiration with lavage, Ringer's solution by hypodermoclysis and intravenous dextrose. At the end of six weeks, fluoroscopy revealed a normally functioning gastro-enterostomy. At the time of presentation, seven and one-half months after the resection, there was no evidence of recurrence or metastases, and the blood was essentially normal: hemoglobin, 18 Gm. per hundred cubic centimeters, and 4,400,000 erythrocytes.

The portion of the stomach resected was 15 cm. in length and weighed 270 Gm. A firm, ovoid tumor, 11 by 7.5 by 6 cm., projected from its anterior surface, 5 cm. from the pylorus (fig. 1). The base of this tumor was broad, 5 by 6 cm., and lay 1 cm. below the lesser curvature and 6 cm. above the greater curvature. There was almost no stalk. Numerous fibrous adhesions appeared on the posterior surface of the stomach. The veins of the smoother anterior surface were distended. The pyloric opening readily admitted the index finger. Within the stomach, the

Fig. 1.—The portion of the stomach resected, showing the exogastric sarcoma. The pylorus is at the left, the greater curvature is below.

rugae and mucosa were normal save at the attachment of the tumor. This irregularly ovoid area, measuring 5 by 3 cm., was reddened, 7 mm. in thickness and of a firm cartilaginous consistency. Three ulcerated openings appeared on its surface from which sinuses led to the central portion of the tumor.

The external surface of the tumor was covered by glistening serosa save on the anterior surface where the omentum was attached. Here were numerous fibrous adhesions and irregular subserosal hemorrhages. The surrounding veins were dilated. On palpation the tumor mass was cystic, and its wall was of uneven consistency. When incised, an irregular central cavity was disclosed, containing about 15 cc. of fluid blood, blood clots and necrotic material. The cavity measured 5.5 by 2.5 by 2 cm. Its wall was lined by a grayish, blood-stained, necrotic material, and was formed by irregular masses of the tumor substance.

Pieces for microscopic study were taken from the junction of the tumor and the stomach wall, the gastric mucosa adjacent to the tumor, the cyst lining and from various portions of the tumor. Sections were prepared and stained with hematoxylin and eosin, Mallory's stain, phosphotungstic acid-hematoxylin, aniline acid-fuchsin with methyl green or Wright's as a counterstain, iron hematoxylin and Mayer's mucicarmine.

The main portion of the tumor was composed of elongated spindle-shaped cells containing fibrils of various sizes and having ovoid nuclei with evenly scattered chromatin and rounded ends (fig. 2). Mallory's stain revealed their noncollagenous character, and the myoglia fibrils were particularly well demonstrated by phosphotungstic acid-hematoxylin. Branching fibrous trabeculae, definitely collagenous, separated the tumor into irregular areas of parallel cells. These were of three general types. In one the typical nuclei predominated, mitoses were frequent and there was but little differentiation. This area was characterized by rapid proliferation. In a second area the individual cells were more evident, mitoses were not so frequent and myoglia fibrils were readily visible (fig. 2). The cells showed more definite differentiation. The third areas presented varying degrees of intergradation between the first two.

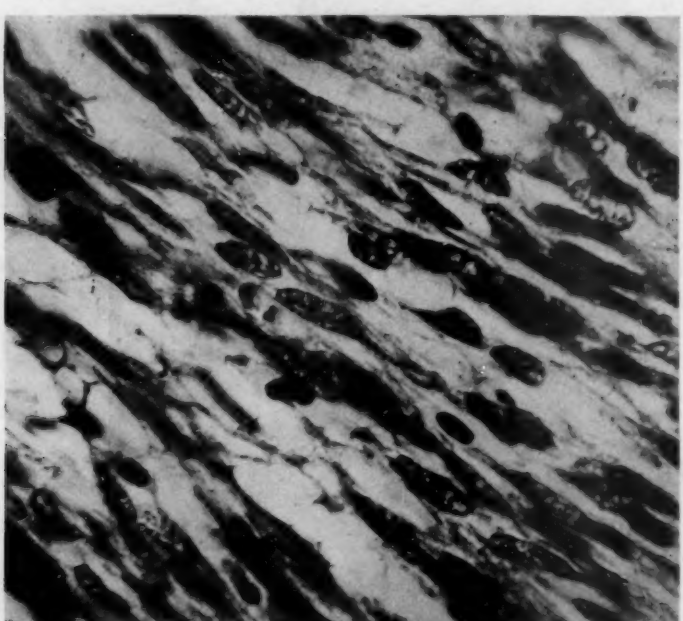


Fig. 2.—High power of a characteristic section presenting the typical tumor cells in an area in which differentiation predominated.

The cavity of the tumor was lined by necrotic tissue, with old hemorrhage. There was no epithelial lining. At its margin the tumor was invading the mucosa. Originating within the muscularis, the groups of spindle-shaped cells had destroyed the overlying muscularis mucosa and were extending into the deeper portion of the mucosa. The gastric mucosa adjacent to the tumor was invaded by a number of leukocytes. Parietal cells were relatively frequent. The interglandular connective tissue was increased.

Ribbert objected to the use of the term sarcoma in connection with neoplasms of muscular origin. McGill's (*Internat. Monatschr. f. Anat. u. Physiol.* **24**:209, 1907) work, however, demonstrated that smooth muscle and fibrous connective tissue originate from similar mesenchymal cells.

The tumor was a slowly growing leiomyosarcoma of the anterior surface of the stomach near the pylorus, originating within the muscularis and without demonstrable metastases.

DISCUSSION

FRANK SMITHIES: Sarcomas of the stomach arise in the ulcer-bearing portions on either wall, and their metastasis is peculiar. With carcinoma there is a disappearance of peristalsis, but with sarcoma the peristalsis is maintained. Hemorrhage is not an important factor. With these points in mind, carcinoma can be eliminated; however, cysts and syphilis of the stomach must be considered.

ACUTE YELLOW ATROPHY OF THE LIVER FOLLOWING ADMINISTRATION OF OXYL IODIDE. S. D. ANDERSON.

Oxyl iodide is a therapeutic product said to be composed of "one part of iodine to five parts of phenylcinchoninic acid, two parts of the latter in chemical union with one part of iodine." This drug, therefore, contains 83 per cent of cincophen and 17 per cent iodine. Reports are found in the literature of eight fatal cases of toxic jaundice following the administration of cincophen or some of its derivatives. The patients examined post mortem died of acute yellow atrophy of the liver, but only two reports are reported in full.

A woman, aged 48, had complained of stiffness, swelling and soreness of the joints of the fingers of both hands. Oxyl iodide in doses of 3 grains (0.195 Gm.) three times a day was prescribed over a period from May, 1928, until January, 1929. During this time, she took approximately 600 (3 grain) tablets. In the latter part of January, edema of the face and the extremities and moderate jaundice developed. She became irrational at times. The urine was greatly reduced in quantity, had a specific gravity of 1.024 and contained albumin and many hyaline and epithelial casts, acetone and diacetic acid but no sugar. The blood showed: red blood cells, 3,600,000; hemoglobin, 62 per cent and leukocytes, 9,200.

A postmortem examination was made twelve hours after death and revealed acute yellow atrophy of the liver, ascites, edema of the lungs, generalized edema of the subcutaneous tissues, and petechial hemorrhages in all of the viscera.

The liver weighed 450 Gm., was flabby, its surface irregular and its color mottled purplish and yellowish brown. The surfaces made by cutting showed numerous circumscribed, raised, yellow areas from 6 to 10 mm. in diameter, against a dark red-brown background. The kidneys were yellow-gray, the cortex swollen and the cortical markings indistinct. The microscopic examination of the liver showed areas of necrosis and hemorrhage beginning about the central veins and extending for varying distances into the lobule. Many entire lobules and groups of adjacent lobules were completely necrotic, and the connective tissue framework of the liver with its bile ducts was collapsed. The bile ducts, therefore, appeared numerous and were separated by loose connective tissue in which hemorrhage had occurred. The kidneys showed cloudy swelling, fatty degeneration and some necrosis of the tubular epithelium. There were no noteworthy changes in the other organs except as indicated in the anatomic diagnosis.

DISCUSSION

R. H. JAFFÉ: It would seem that susceptibility of the liver must be some factor here, because cincophen derivatives are used extensively in medicine without untoward effects. Is it possible that some other cause has induced the changes of the liver?

E. R. LONG: Have animals been tested to see if the compound has toxic properties?

EDWIN F. HIRSCH: Were qualitative or quantitative chemical tests made?

A CASE OF RHINOSPORIDIUM SEEBERI IN A RESIDENT OF THE UNITED STATES. MARY C. LINCOLN and STELLA M. GARDNER.

This paper appears in full in this issue, p. 38.

DISCUSSION

EDWIN F. HIRSCH: The lesions illustrated resemble those of coccidioidal granuloma in certain respects.

CLINICAL AND PATHOLOGIC ASPECTS OF APPENDICITIS. BERNARD PORTIS.

Appendicitis is the most frequent of all pathologic conditions of the abdomen. The rotation of the cecum during embryonic development explains the various positions which the appendix may assume.

Most of the 135 cases of acute appendicitis were apparently hematogenous, and about 25 were associated with some form of infection of the upper respiratory tract. A local origin from a small ulceration, however, was also considered a cause. The earliest microscopic changes are hyperplasia of the lymph follicles and raising of the lining epithelium by a serofibrinous exudate. Somewhat later the exudate infiltrates the wall or enters the lumen. Gangrene and perforation may then occur. Resolution is the most favorable outcome, but most cases which have reached the suppurative stage rarely subside.

Many of the patients operated on for acute appendicitis were seen late after the onset and frequently had been subjected to drastic purging. In spite of this, there were only four deaths from peritonitis. The clinical features were somewhat dependent on the age of the patients. In young children the symptoms were bizarre, while in older children the symptoms were similar to those of adults. The onset was never sudden, but developed to an acute intensity in several hours. In 75 per cent of the cases the pain was generalized and localized only to the right lower quadrant after several hours. Backache was severe when the appendix was retrocecal. Gastro-intestinal distress was present in all cases. In a few it manifested itself simply by anorexia, while nausea and vomiting occurred in 77 per cent. Fever was present usually at the end of twenty-four hours. The leukocytes of the blood were increased usually to from 15,000 to 20,000. There were, however, four patients with gangrene of the appendix without leukocytosis. Localized tenderness was constant, but rigidity was often absent.

Chronic appendicitis is usually not inflammatory but is produced by adhesions and kinking of the appendix with interference to the normal peristalsis. The symptoms may simulate any of the chronic inflammatory conditions of the gastro-intestinal or bile tract.

Book Reviews

DEGENERATION AND REGENERATION OF THE NERVOUS SYSTEM. By S. RAMÓN Y CAJAL, M.D., F.R.S., Director of the Instituto Cajal, Madrid, Honorary Professor of Pathology in the University of Madrid. Translated and edited by Raoul M. May, Ph.D. (Harv.), D. ès Sc. (Paris). Two volumes. Pp. 769, with 317 illustrations. New York: Oxford University Press, 1929.

This great work, which was published in Spanish in 1913 and 1914, is described by the author in his preface to the present translation as practically "unpublished in Europe and North America." As a testimonial to the distinguished author, on the occasion of his receipt of the Nobel Prize, the physicians of the Argentine Republic asked permission to publish at their own expense a memoir containing his researches, and these two volumes were prepared for that purpose. It is not a reprint of previous publications, but an entirely new work, representing much additional research directed especially toward this end. Nearly all the copies of the Spanish edition were distributed to the South American subscribers; hence, the work has been difficult of access by the rest of the world. The translator and the Oxford Press have performed a great service and both have done their work extremely well. An excellent portrait adds a welcome personal touch.

The book contains the ripest fruits of a wide experience in a difficult and controversial field. The theories of nervous degeneration and regeneration are interwoven with those of the histogenesis of nerve fibers, and the work opens with a sketch of the historical development of these ideas with a critical analysis of the evidence. These controversies may be regarded as closed so far as the major issues are concerned.

"The doctrine of the neurone, intimately connected in the pathological field with the theory of continuity, came out of this new crisis strengthened and victorious. Instead of finding, in the field of nervous regeneration, insuperable difficulties, it found, on the contrary, new and peremptory demonstrations, in whose light not a few of the enigmatic phenomena of the morphology and growth of nervous protoplasm are beginning to be understood."

These words at the close of the first chapter indicate the general point of view, and the remainder of the work is devoted chiefly to factual description of the author's own preparations, with full citation of the work of others. It is impossible here to summarize these observations, which are presented in a clear and convincing way. Chapter XVI, at the close of the first volume, summarizes the "General Theoretical Interpretation of the Phenomena of Nervous Regeneration" in a succinct statement of the leading facts and their bearing on the author's theory of neurotropism.

The second volume is devoted entirely to degeneration and regeneration of the nerve centers, including the sensory and sympathetic ganglions, the spinal cord and the brain. This is of special interest to neuropathologists, for it records much experimental work not widely known in this country. As in the first volume, the citations of the literature are full, critical and extremely helpful.

The doctrine of neurotropism is the most important theoretical conclusion of the entire program, and constant references to it are made throughout the book. This conception is founded on the belief that in the peripheral nerves there is a symbiotic relation between the axon of the neuron and the sheath cells, and in the nerve centers, including all peripheral ganglions, neuroglia and satellite cells are related to neurons in a somewhat similar way. In the second volume (p. 459), he elaborates the hypothesis of the disequilibration of the neuroneuroglial symbiosis.

"On various occasions we have pointed out the fact that the neurone, far from living independently, becomes dynamically and trophically associated with certain cells of a special nature, among which we include the *protoplasmic neuroglia* of

the centers, the *satellite cells* of the ganglia (*amphicytes* of v. Lenhossék) and the *cell of Schwann* of the nerves. The two categories of elements are mutually serviceable, and there is established between them something like a symbiosis comparable to the well-known symbioses of fungi and algae to form lichens, or of the hydra and its chloroplasts.

"In a normal state, that is, when the reciprocal actions are in equilibrium, the satellite cells are few. They abstain from proliferating and they respect the neuronal morphology. This quiescence is perhaps due to the paralyzing action of some principle which is liberated, under normal conditions, by the young and robust neurones. When these become fatigued, however, or when they weaken or die, the antimitosogenic check is moderated or suspended, and the satellite cells therefore multiply and press upon the periphery of the neuronal soma, forming in it pits and even holes, handles, fenestrations, etc. Moreover, the growing pressure of the satellite cell, or of the daughter cells proliferated from it, also brings about, through a mechanical or chemical stimulus, more or less important neoformative processes."

In the regeneration of peripheral nerves it is demonstrated that the cell of Schwann is not necessary for the genesis and growth of the axons. Yet the proliferation of these cells plays a significant part — indeed, a necessary part — in the regenerative process.

"The nervous reunion of the peripheral stump and restoration, without physiological errors, of the terminal nerve structures, are the combined effect of three conditions: the neurotropic action of the sheaths of Schwann and terminal structures; the mechanical guidance of the sprouts along the old sheaths; and, finally, the superproduction of fibers, in order to ensure the arrival of some of them at the peripheral motor or sensory organs" (p. 371).

In pathologic states of the ganglions and the central nervous system all the satellite cells and certain glial elements, necrosed or degenerating neurons, exudates with their leukocytes, etc., have some stimulating or neurotropic influence. But none of these have the potency of the proliferating cells of Schwann and, for this and other reasons, regenerative activities in the nerve centers, which are described in great detail, are abortive so far as restitution of normal function is concerned.

What may be the real nature of the reconstructive neurotropic influence is not revealed by any evidence so far available. Cajal writes (p. 392):

"It is difficult, in the present state of knowledge, to imagine what is the nature of the stimulating substance. As a tentative hypothesis we have supposed that the substance contained in the sheaths of Schwann of the peripheral stump should be conceived, not as a fixed, quiescent principle, capable of being neutralized like an alkali by some acid substance within the cone of growth, but as a ferment or catalytic agent which stimulates the assimilation of the axonic protoplasm and which does not become used up while acting on the nervous protoplasm."

In the earliest stages of regeneration, while the axonal sprouts are pushing out without guidance by neurotropic or other influences, the activity which they manifest is regarded (following Heidenhain) as due to an intrinsic histodynamic impulse which is a growth process not dependent on any specific material substance or soluble enzyme. This active metabolism of the early axonic sprouts seems to the reviewer to be related to the physiologic gradients of Child, both in its intrinsic nature and in its reactions to the surrounding medium. This applies also to the neurotropic influence of cells of Schwann, satellite cells, etc., in later stages of regeneration. Active metabolism excited by trauma, or otherwise, gives to the activated regions a physiologic dominance the mechanism of which is not fully understood but the manifestations of which are sufficiently similar to the phenomena described by Child in nonnervous protoplasm to justify further examination from this point of view.

The work of Cajal and his co-workers has led to a renaissance of neuropathology, and the further development cannot now be forecast. These volumes will do much to hasten this development in all English-speaking countries.

OLD AGE. THE MAJOR INVOLUTION. THE PHYSIOLOGY AND PATHOLOGY OF THE AGING PROCESS. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Price, $3. Pp. 199, with 29 illustrations. New York: Paul B. Hoeber, 1929.

The Wesley M. Carpenter Lecture of 1928 (Bull. New York Acad. **4**:1006, 1928; New York State J. Med. **28**:1349, 1928) forms the nucleus of this monograph. After the delivery of the lecture and its publication, the many requests for reprints indicated that the conception of old age advanced in the lecture was arousing a good deal of interest. This central conception remains unchanged, but additions and alterations have been made to clarify and strengthen the conception and the conclusion to be drawn from it. Most of the new matter consequently relates to involution as a physiologic process and function, because the central idea in this discussion of old age is that it should be regarded as essentially physiologic and as a normal major involution and not as a pathologic process. In the preface, the author states that "to his surprise a certain minority of his correspondents, while accepting the view put forward as rational and based on scientific facts, expressed themselves as 'having been depressed' by the philosophic conclusions inevitably deducible from such a view point." Just the opposite result was in the writer's mind—"the presentation of a rational workable philosophy of old age as an antidote to the modern futilities of life-extension of the individual to extreme limits and of possible rejuvenation." The first third of the book deals with the evolution and maturity of the "human machine," and the rest with old age—the major involution—under the following headings: The Functional Changes of Senescence; The Picture of Fully Developed Senility; The Primary Tissue Changes of Senescence; The Secondary Pathologic Changes of Old Age; The Concentration of Disease in Different Life Periods; Termination of the Involution Process in Normal Death; Pathologic Death; Theories of Senescence; Extension of the Life Limit; Rejuvenation; A Philosophy of Age. As perhaps might be expected under the circumstances, man as distinguished from woman rather monopolizes both the text and the illustrations, but it is made clear that the same general principles apply in both cases. The discussion of the normal limits to the duration of life is illuminating. The book is readable and instructive. The style is vigorous. The reasons for regarding old age as essentially the result of a normal physiologic process are set forth convincingly, and the signifiance of this conclusion in one's outlook on life is indicated clearly. The pathologist teaches a philosophy of life that will commend itself to the intelligent reader.

A MANUAL OF HELMINTHOLOGY MEDICAL AND VETERINARY. By H. A. BAYLIS, M.A., D.Sc., Assistant Keeper, Department of Zoology British Museum. Price, $10. Pp. 303. New York: William Wood & Company.

Interest in parasitology has been widely aroused during recent years, and medical and veterinary men are more and more realizing the true importance of the affects on public health and on that of the domestic animals as caused by the flatworm, tapeworms and roundworms. Parasitology has formerly been considered to be of importance only to the tropics and subtropics; now its importance is recognized in all parts of the world. At this critical time this handbook of helminthology appears and will find a ready demand. It is broadly limited in its scope to those helminthes affecting man and the animals with which he may come in contact, including nearly all parasites of man and the domesticated animals of the world. This is particularly useful in this era of international travel and commerce, because one may at any time encounter forms of parasites new to one's own country or recently introduced. This book will help one to identify them.

It is written in a clear concise style with sufficient explanation to allow any educated man to use it successfully even though he lacks in knowledge of parasitology. The 200 figures aid a great deal in ready understanding. The information is reliable, and there is much evidence that the author has often turned to the original source material for information or illustration.

The classification used is the latest and best available, while in many instances the better known synonyms are also given. Poche has been followed in the classification of the trematodes and cestodes. It is questionable whether his larger groupings will find favor with parasitologists, but in many instances it is a decided improvement over older classifications, and it offers those generic and specific names which are most nearly in accordance with the international laws of nomenclature. Introductions and explanations are provided for each of the three divisions, the trematodes, the cestodes and the nematodes, while every smaller division is carefully defined. A general index and an index of hosts and their parasites greatly enhance the usefulness of this book.

It is a good textbook, but the price will prevent its general adoption for student use. However, it should find sale and be used extensively by the professions because it is an excellent reference book, a most worthy addition to the library of physicians, veterinarians, public health workers, parasitologists and zoologists.

The publishers have provided first quality paper and presswork in an attractive and substantial binding.

COLLOID CHEMISTRY. THEORETICAL AND APPLIED. By Selected International Contributors. Collected and Edited by Jerome Alexander. Vol. 2. Biology and Medicine. Price, $15.50. Pp. 1,029. New York: The Chemical Catalog Company, 1928.

It is a fact, recognized by all who are familiar with the advances of modern science, that the more extensive and complex science becomes, the more narrowly do its devotees restrict themselves to highly specialized fields. This is especially true in the biologic sciences, in which theoretical advances have lagged far behind experimental observation and in which, consequently, one finds few of those great generalizations which serve to collect and coordinate isolated facts. The present tendency to explain vital processes by means of chemical and physical laws finds its greatest justification in the great strides which have been made in biology and medicine by the application of physicochemical methods. The present volume emphasizes the relationship between colloid chemistry and biology. Even the most casual reader of this book cannot fail to be impressed by the wide variety of contacts between the two fields, as evidenced by the titles of the papers presented. Thus one finds papers ranging from such general topics as proteins, enzymes, cell structure, protoplasm, fertilization, and micro-organisms to the more specifically medical provinces of serology, tuberculosis, malignant tumors, immunity and pharmacology. One cannot help feeling that colloid chemistry is the link which connects the various biologic sciences and that it represents the borderland not only between the various biologic sciences but also between those and the physical sciences. At the same time one is led to hope that future advances in this border field will lead to important clues concerning the structure and functional activity of protoplasm itself.

This volume, like its predecessor, consists of papers by selected contributors, each paper being a resumé of work done by the author and others in that particular field. The authors and their subjects have been chosen so as to be representative of the field covered. Besides containing numerous references to the original literature, each paper contains, in footnotes, comments by the editor and references to other papers both in this volume and in the first volume of this series, which deals with the more fundamental aspects of the subject. This book will prove a revelation to those medical students who have acquired the idea that there really is some connection, however mysterious, between colloid chemistry and medicine. It should prove valuable to those investigators who are anxious to know what contributions, if any, colloid-chemical methods may be expected to make to their particular fields. And to the general reader of biology and medicine, it should prove especially interesting as an indication of the trend of modern biologic thought.